Estimation of the number of people with Down syndrome in Europe

SUPPLEMENTARY MATERIALS

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S1. Number of potential and actual LBs of children with DS 1950–2015

S1A. Estimates of nonselective LBs of children with DS after 1950

The number of children with DS that would have been born in the absence of elective terminations can be estimated on basis of maternal age distribution in general population by applying a model of maternal-age specific chances for a LB of a child with DS to these data.

We used the most recent model of maternal-age specific chances, based on the largest sample, developed by Morris et al. (2002). First, we constructed 5-year maternal age-specific chances by year of birth by applying the single-year chances from the model of Morris to the U.S. birth data with single-year maternal age bands, available from 1950 onwards (and before) in the Vital Statistics of the United States (https://www.cdc.gov/nchs/products/vsus.htm) The 5-year maternal age-specific chances evolve slightly over the years in the U.S. sample (as the maternal age distribution within these 5-year bands changes over time), and we have assumed that this would apply to the European samples, too. The use of these constructed 5-year maternal age-specific chances by year of birth is fine-tuning with only slight effects on the estimates of the LBs of children with DS.

Netherlands
For the Netherlands, the National Office for Statistics, (in Dutch: Centraal Bureau voor de Statistiek (CBS)) provides data on maternal age by single year band available from 1950 onwards, and on maternal age in 5-year bands from 1936 onwards (see S1B).

United Kingdom
For the UK, data on births by maternal age were available from the Office for National Statistics (ONS), National Records of Scotland (NRS), and Northern Ireland Statistics and Research Agency (NISRA) in single-year maternal age bands, for all parts of the UK from 2002 onwards, for Scotland from 1950 onwards, and for Northern Ireland from 1974 onwards. The data were available in five-year bands for England/Wales from 1938 onwards, for Scotland from 1939 onwards, for Northern Ireland (NI) from 1974 onwards, and for NI for 1960/1961 (see S1B). If available, we used single-year bands.

For NI, we have interpolated live birth prevalence estimates for the period 1961–1974. For estimating NI LB prevalence of DS before 1960, we have used the relation between LB prevalence estimates for NI and England/Wales between 1960–1976. For this period, LB prevalence estimates for NI could be predicted almost perfectly by LB prevalence estimates for England/Wales (R^2=0.99). We applied the regression equation to LB prevalence estimates for England/Wales before 1960 to predict live birth prevalence of NI for this period. Before 1960, the predicted LB prevalence for NI was around 40% higher than the LB prevalence estimates for England/Wales, which was also the case in 1960/1961 on basis of the Census data of NI (see S1B).

Other European countries
For other European countries, we found two different databases on maternal age distribution. The first is the World Population Prospects of the United Nations (see S1B). The second is the United Nations Statistics Division (see S1B).

The first presents estimates for 233 countries and areas. The Population Division of the United Nations states that half of those countries or areas do not report official demographic statistics with sufficient detail. In addition, according to the Population Division, official national statistics are not

perfect, but affected by incompleteness of coverage, lack of timeliness and errors in the reporting or coding of the basic information. The Population Division tries to fill in the gaps and to resolve inconsistencies by using a systematic cohort-component method (the method is presented in (https://population.un.org/wpp/Publications/Files/WPP2017_Methodology.pdf).

The second data are the official national statistics, as reported to the United Nations Statistics Division. However, these are not available for all years, or for all countries. Especially for many former East bloc countries, data are lacking before 1990. In addition, reported data might be less reliable for some countries. Yet, in general, comparing the datasets, the differences between estimates of LB prevalence of DS on basis of the data from national statistical offices (as reported to the United Nations Statistics Division), if available, and the estimates on basis of the Population Division are small and not systematic.

An exception appears to be the UK, for which estimates of number of LBs of children with DS on the basis of statistical offices in the UK (see the paragraph on the United Kingdom above) are systematically higher in the period before 1970 than the estimates of the Population Division (13% to 19% for the five year periods between 1950 and 1970). Perhaps, this difference is the result of the UK only starting to report national data on maternal age distribution to the United Nations since 1982 (first available year for the UK in the United Nations Statistics Division), so the Population Division may have been forced to estimate for the UK with a serious lack of empirical information for less recent years.

However, we would expect reported statistics by the statistical offices in the UK to be fairly reliable, probably already in the 1950s and 1960s; as such, we have used their data (see S1B). As stated above, we also used national statistics for the Netherlands; however, these are very similar to the estimates of the Population Division.

For the other European countries, we have chosen to use the estimates of the Population Division, as these are available for the whole period for all years and might be of a higher quality for some countries.

S1B. Sources for maternal age distribution after 1950

Netherlands
Table: “Birth; age mother (on 31-12), birth order and fertility rates 1950-2014”; and “Population, households and population dynamics, from 1899”
http://statline.cbs.nl/Statweb/publication/?DM=SLEN&PA=37744eng&D1=a&D2=0-35&D3=0,50,55,60,63-64&LA=EN&HDR=T&STB=G1,G2&VW=T; and
http://statline.cbs.nl/Statweb/publication/?DM=SLEN&PA=37556eng&D1=3-8,65-69,90-95,180,182-183,189-190&D2=37&LA=EN&VW=T retrieved 22-Nov-2018.

United Kingdom
Great Britain (England, Wales and Scotland). Livebirths by age of mother, 2002-2014, Great Britain. Source - Office for National Statistics. Produced by Demographic Analysis Unit, ONS
https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/adhocs/004976livebirthsbyageofmother2002to2014greatbritain/birthsbysingleyearofageofmother20022014gb_tcm77-426362.xls (retrieved 22-Nov-2018).
England/Wales: Dataset Name: PBH31A Type of Dataset: Cross-sectional. Description: Live births: Age of mother in 5-year age-groups: within/outside marriage and sex 1938-2004 a. all live births and female births only. Birth Statistics : Historical Series of Statistics from Registrations of Births in England and Wales, 1837-1983. ONS (received by email from ONS in 2006);

Scotland: Table BT.2: Births, by mother's age, Scotland, 1945 to 2015 on https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/births/births-time-series-data (retrieved 22-Nov-2018).
Northern Ireland: https://www.nisra.gov.uk/publications/live-births-by-single-year-age-mother-and-marital-status-1974-2015 (retrieved 15-Sept-2018) and https://www.nisra.gov.uk/publications/registrar-general-annual-report-2015-birth-tables (retrieved 23 -Nov-2018). Table 3 in Census of Population 1961, Fertility Report, Government of Northern Ireland. https://www.nisra.gov.uk/publications/1961-census-reports (retrieved 23-Nov-2018).

Other European countries
File FERT/6: Births by five-year age group of mother, region, subregion and country, 1950-2100 (thousands) in the World Population Prospects of the United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, DVD Edition. https://population.un.org/wpp/Download/Standard/Fertility/ (retrieved 9-Nov-2018); and Live births by age of mother and sex of child. Demographic Statistics Database, United Nations Statistics Division. http://data.un.org/Data.aspx?q=live+births+mother&d=POP&f=tableCode%3a260 (retrieved 21-Sept-2018)

S1C. Estimates of actual LBs of children with DS

Prenatal screening, if followed by elective DS-related termination, changes the actual LB prevalence of DS in recent years. To fill in the gap, we have collected as much data as possible on actual numbers of LBs of children with DS in the different countries. For some countries, we found additional data (for instance, the number of invasive procedures, numbers of children with DS in hospital, or number of deaths of young children with DS), which can be used to estimate the impact of screening and the LB prevalence in a more indirect way (details are explained in the notes by country). Sources by country are described in S1D.

Before 1967, in any country, the effect of prenatal diagnostics on the LB prevalence of DS will have been zero. In addition, we think that in the period 1965–1970, the reduction in LBs of children with DS resulting from prenatal diagnostics, followed by elective terminations, was still very low. De Graaf et al. (2015) (doi: 10.1002/ajmg.a.37001) have estimated this to be less than 1% in the period 1965–1970 for the U.S.; we have modeled similarly for Europe.

For some countries data on LBs of children with DS are available from the 1980s onwards. If available, we have estimated the reduction percentage as of 1980; for the period before 1980, we have extrapolated linearly to 0% in 1967. If data were available from 1985 onwards, we have estimated the reduction percentage as of 1985 and extrapolated linearly to 0% in 1967, etc. If data for the most recent years were not available, we have projected trends in reduction percentage in preceding years.

For many countries only regional data were available (through EUROCAT mostly). In the explanations by country below, we have added information on which percentage of national births were covered by the regional data If full national data were available, we made use of these. If only regional data were available, we pooled these by country and made use of 5-year running averages to minimize random fluctuation, which is to be expected in small populations.

Western Europe

Austria

We used EUROCAT data for Styria (1985–2012) (see S1D for details on the sources). For the period 1985–2012, these data cover on average 14% of the general births in Austria, varying between 13% for 2010-2012 to 15% for 1985–1989.

Belgium

We used data from two Belgium EUROCAT regions, pooled with data for Flanders from "Child and Family" (Kind en Gezin). For the period 1980–2014, the data cover on average 27% of the general births in Belgium, varying between 7% for 1980–1984, 27% for 2000–2004, 34% for 2005–2009, and 64% for 2010–2014.

France

We used pooled EUROCAT data from 6 different regions. For the period 1980–2014, the data cover on average 17% of the general births in France, varying between 13% for 2011–2014 to 21% for 1990–1994 and 1995–1999.

For 2010-2015, national postnatal and prenatal data from the l'Agence de la biomédecine are available. The Agency reports how many prenatal diagnoses of children with DS result in LBs. We have assumed that in cases with unknown pregnancy outcome (on average 12% of the total number of prenatal diagnoses of DS, the percentage LBs is similar to that in cases with a known outcome. Furthermore, as the period between a prenatal diagnosis (at 3 months gestational age) and birth is approximately half a year, we assumed that half of the children diagnosed prenatally in a particular calendar year, with LB as pregnancy outcome, were born in that same calendar year and the other half in the next calendar year.

These national data include births in the French overseas territories (4% of general births). In the EUROCAT data for 2010-2015, the LB prevalence for DS is on average 6.0 per 10,000 LBs in the European parts of, but around 10.5 per 10,000 in the two overseas territories under observation. We have assumed that there were 10.5 per 10,000 DS LBs in all overseas territories in this period. We have multiplied the total number of general births in the overseas areas with this prevalence estimate (10.5 per 10,000), and subsequently subtracted the estimated number of LBs with DS in these areas from the national numbers, as we are focused on the LBs of DS in the European parts of France.

For 2010, the LB prevalence estimates based on EUROCAT is similar to the estimate based on the national data (national data are 2% higher). However, for 2011-2015, the estimates based on national data are 24% higher than estimates based on regional EUROCAT data. As we consider the national based data to be more comprehensive, we use these from 2010 onwards.

Germany

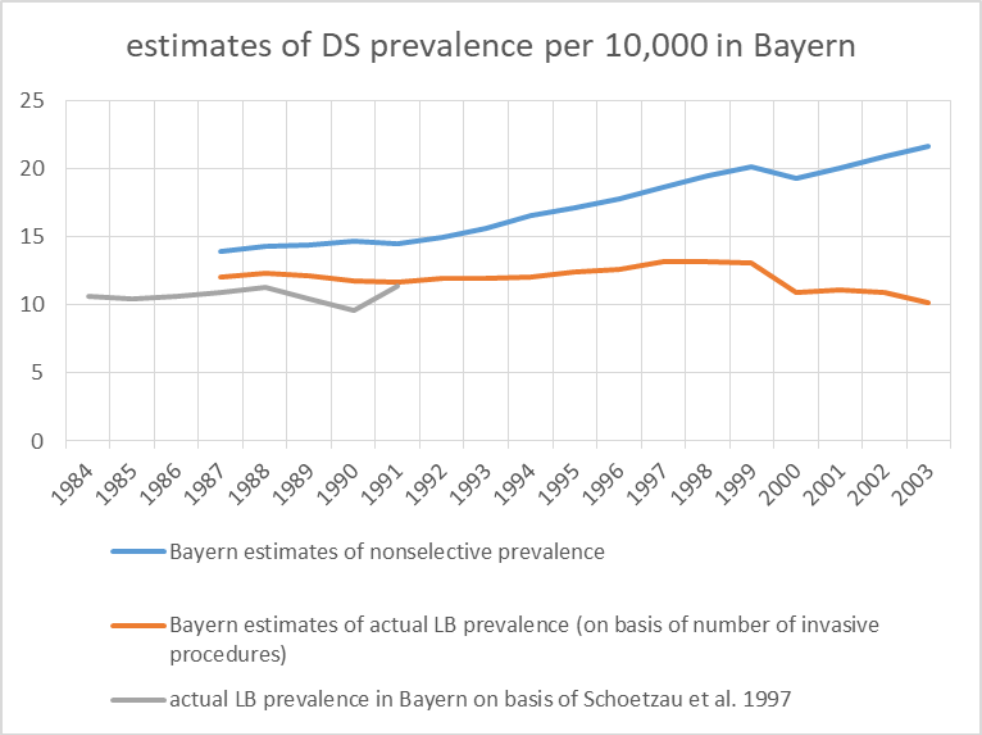
EUROCAT data for Germany cover two areas only, representing around 3% of all births in Germany. Of these two areas the largest is Saxony-Anhalt, a former East German region. Of the nonselective births of children with DS (estimates based on maternal age distribution), around 14% in 2015 would be from the former East German regions and 86% from the former West German regions (and 11% were from the East part in the 2000s). In addition, former East German regions might be culturally different from former West Germany, with both a different maternal age distribution and possibly a different uptake of prenatal screening and diagnostics. Though we could find relatively recent additional data from Mecklenburg-Vorpommern for 2002–2004, this also is a former East German region.

However, we could find information on the number of prenatal invasive procedures for (former) West Germany as a whole, for 1970 (6), 1976 (1,796), 1982 (15,883), 1987 (36,000), 1993 (56,594) and 1995 (60,000), and for one West German region (Bayern, covering around 91% of all births in Bayern) for 1987–2003 (from 3,436 in 1987 increasing to a peak of 10,883 in 2000, slightly decreasing to 9,637 in 2003.

As Bayern has the most recent and the most detailed data (that is, these data are divided into amniocenteses and CVS), we examined these first. For 1995–2003, nonselective prevalence for DS in Bayern can be estimated on basis of maternal age data from the Statistische Ämter des Bundes und der Länder, Deutschland. The data on CVS and amniocenteses for Bayern, based on BAQ (Bayerischen Arbeitsgemeinschaft für Qualitätssicherung in der stationären Versorgung) contain information on the percentage of all pregnant women that are 35 years of age or older. We projected the relation between this percentage and the estimates for nonselective prevalence for the period 1995–2003 on the percentages of pregnant women of 35 years of age for the years 1987–1994 to estimate the nonselective prevalence in Bayern for 1987–1994. As not all (but around 91% of the births) in Bayern, were covered in the BAQ data, we projected the estimates of nonselective prevalence by year on the data on number of births from the BAQ, to estimate the number of LBs of children with DS that would have been born absent elective terminations in the births surveyed by BAQ.

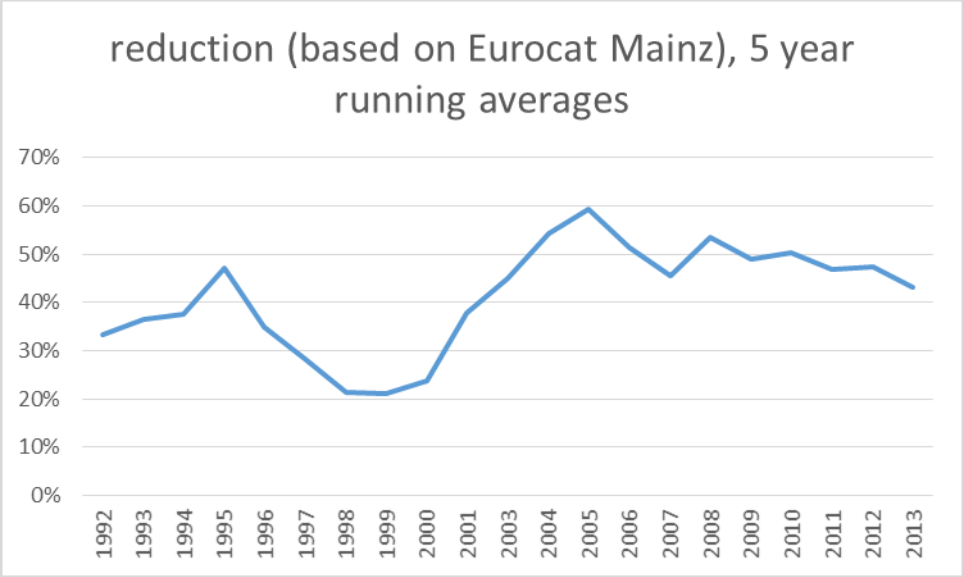
The next step was to estimate how many births of children with DS were prevented as a result of CVS and amniocentesis, which was followed by an elective abortion. To model this, we made use of Dutch data from WPDT-reports (Annual reports of the Working Party Prenatal Diagnosis and Therapy)—which are complete—on the total number of amniocenteses and the total number of elective terminations of fetuses with DS after amniocentesis, and the total number of CVS and the total number of elective terminations of fetuses with DS after CVS by year, in the Netherlands for the period 1991–2003. (For the years before 1991, we applied the average of the Dutch data for 1991–1993.) The relation between the number of amniocenteses/CVS and the number of children with DS that were aborted changes in time, as advancements in technical characteristics of screening allow a more precise assessment of risk. We assume that this development is similar in the Netherlands and Germany, and we assume that continuing a pregnancy after a prenatal diagnosis in this period was similarly rare in both the Netherlands (WPDT-reports) and Germany. The relation between total number of amniocenteses and number of DS-related terminations in the Netherlands by year (using running 3-year averages), was projected on the number of amniocenteses as registered by BAQ in Bayern, and we followed the same procedure for CVS to produce an estimate of the number of DS-related terminations in the births covered by BAQ. As not all DS-related terminations would have ended in a live birth in absence of elective terminations—as some (around 27%, see De Graaf et al. ,2015; DOI 10.1002/ajmg.a.37001) would have ended in a natural miscarriage—we assumed that 73% of the elective terminations is a measure for the number of births that were prevented. By subtracting the prevented births from the nonselective births, and dividing this by the total number of live births in the population multiplied by 10,000, we could estimate actual prevalence in Bayern.

For 1984–1991, Schoetzau et al. (1997) estimated Bayern's DS LB prevalence on basis of a systematic analysis of hospital reports on diagnoses in young children. These estimates, for the overlapping years 1987–1991 are on average 10% lower than our estimates (range 2% to 14%), which might result from underascertainment in the hospital data and/or impreciseness in our estimates (see the Figure below). We consider a deviance of this magnitude small enough to continue with an estimation for West Germany as a whole.

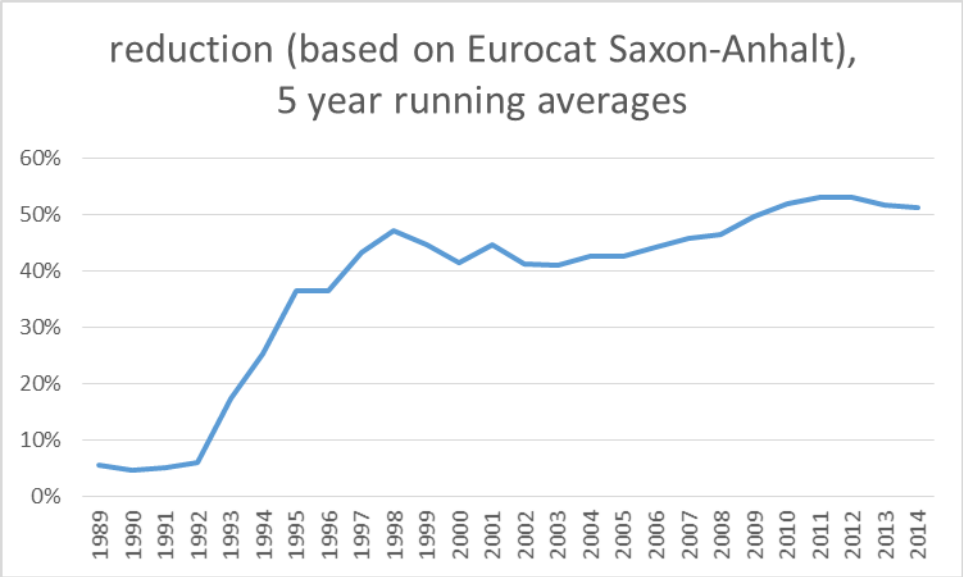


As mentioned earlier, we have obtained information on the number of prenatal invasive procedures for (former) West Germany as a whole, for 1970 (6 procedures), 1976 (1,796), 1982 (15,883), 1987 (36,000), 1993 (56,594) and 1995 (60,000). According to our sources, these procedures were all amniocenteses for 1970, 1976, and 1982. For the years 1987, 1993, and 1995, we assumed that the percentage of CVS of all invasive procedures was similar to the percentages in the BAQ data from Bayern for the corresponding year. We then followed the same procedure as described above for the BAQ data, by projecting the Dutch relation between number of amniocenteses/CVS and number of DS-related terminations after an amniocentesis/CVS on the data from West Germany and correcting for natural miscarriages. This produced an estimate of the number of births with DS that were prevented in West Germany. On basis of data on maternal age in West Germany, we estimated nonselective numbers. Combining these two estimates yields an estimate of the reduction percentage in West Germany: around 0% in 1970, 1% in 1976, 11% in 1982, 23% in 1987, 31% in 1993, and 37% in 1995. If we compare these estimates with estimates based on the difference between nonselective prevalence in West Germany (based on maternal ages) and LB prevalence estimates based on pooled counts of LBs of children with DS from Berlin (1980–1989), Bayern and Northern Bayern (1984–1989), we find similar percentages. For the pooled counts, there was an 11% reduction for 1980–1984 and 25% for 1985–1989. For 1987, 1993 and 1994, the reduction estimates based on the number of invasive procedures in West Germany turn out to be slightly higher than the estimates we had made for Bayern for the corresponding years: for 1987, there was a 23% reduction in West Germany versus 14% in Bayern; for 1993, 31% versus 23%; and for 1995, 37% versus 28%—an 8 to 9 percentage points difference. Lower reduction corresponds with slower uptake of screening, which probably reflects the fact that Bayern is a rather conservative Christian region. For the last five years with data (1999–2003) in Bayern, reduction was estimated at 45%. If reduction percentage in West Germany, as a whole, was again around 8 to 9 percentage points higher, this would have been 53–54% around 2001.

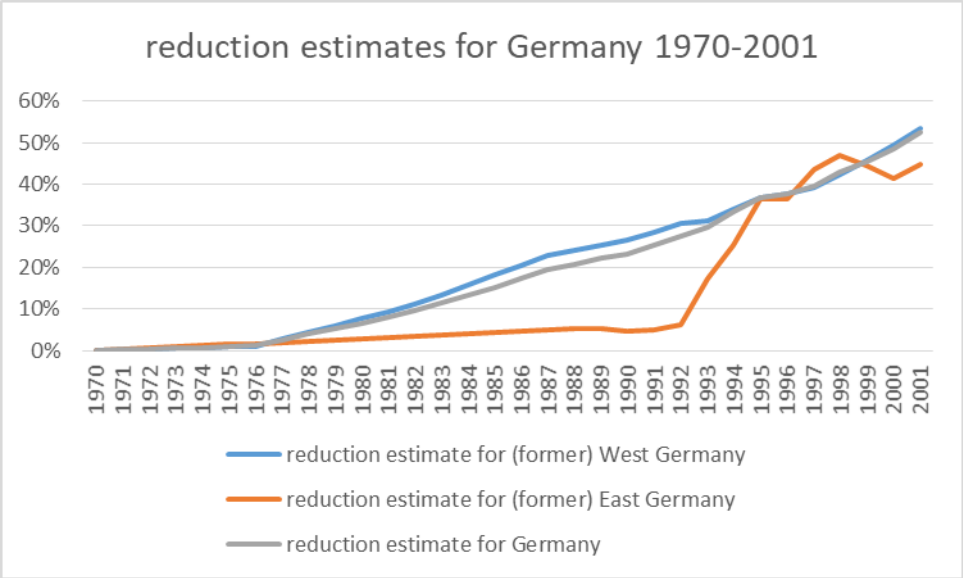
For comparison, we present the development of reduction percentage in the only West German EUROCAT region Mainz. EUROCAT registers LBs and elective terminations separately. The nonselective number that would have been born in absence of elective terminations can be estimated by adding 0.73 x terminations (as not all would have been a LB absent elective terminations) to the LBs. Reduction can be estimated by dividing (0.73 x terminations) by the nonselective number. To minimize random fluctuation, we used five-year running estimates—that is, we pooled together all data from 1987–1991 to construct the numbers for 1989, etc. The results are in the Figure below. It shows an around 50% reduction for the period 2003–2013. However, as it is a small region, some random fluctuation is to be anticipated.



For assessing the development of reduction percentage in former East Germany, we looked at the EUROCAT data from Saxon-Anhalt, available from 1987 onwards. We used the same procedure as described above for Mainz. The results for Saxon-Anhalt are in the Figure below. It shows a 40–45% reduction in the late 1990s and 2000s and around a 50% reduction in 2010–2015.

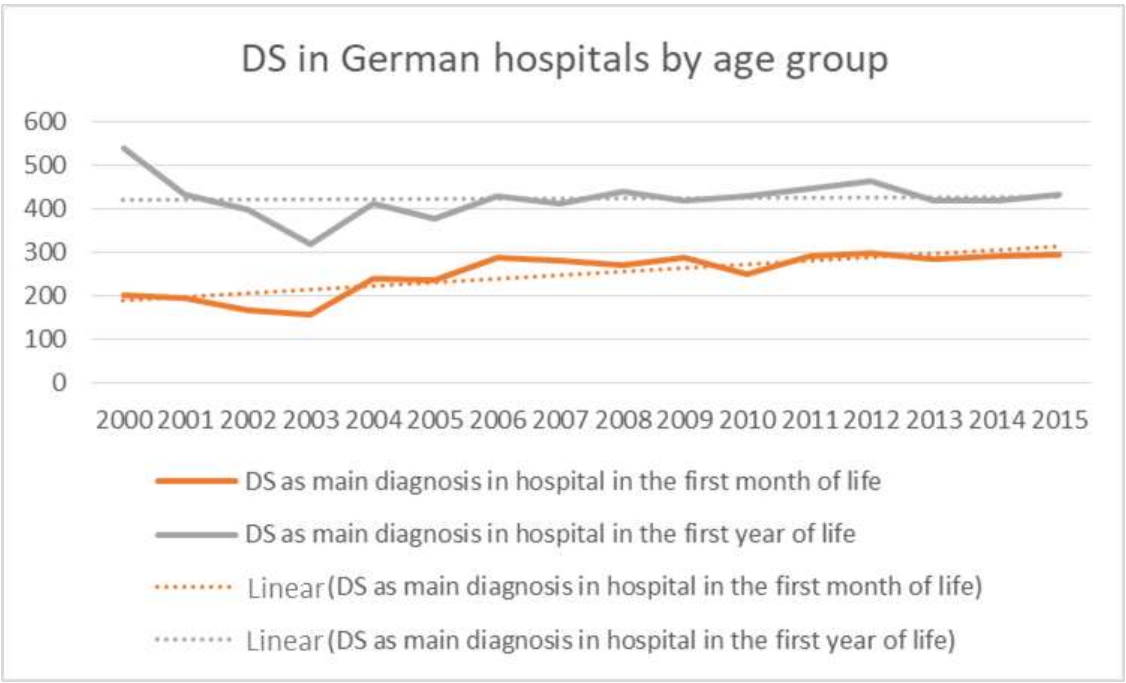


Pooling all the information from the preceding paragraphs together, extrapolating in-between years, we could construct the graph below, with reduction percentage for DS, resulting from elective terminations, for the period 1970–2001.

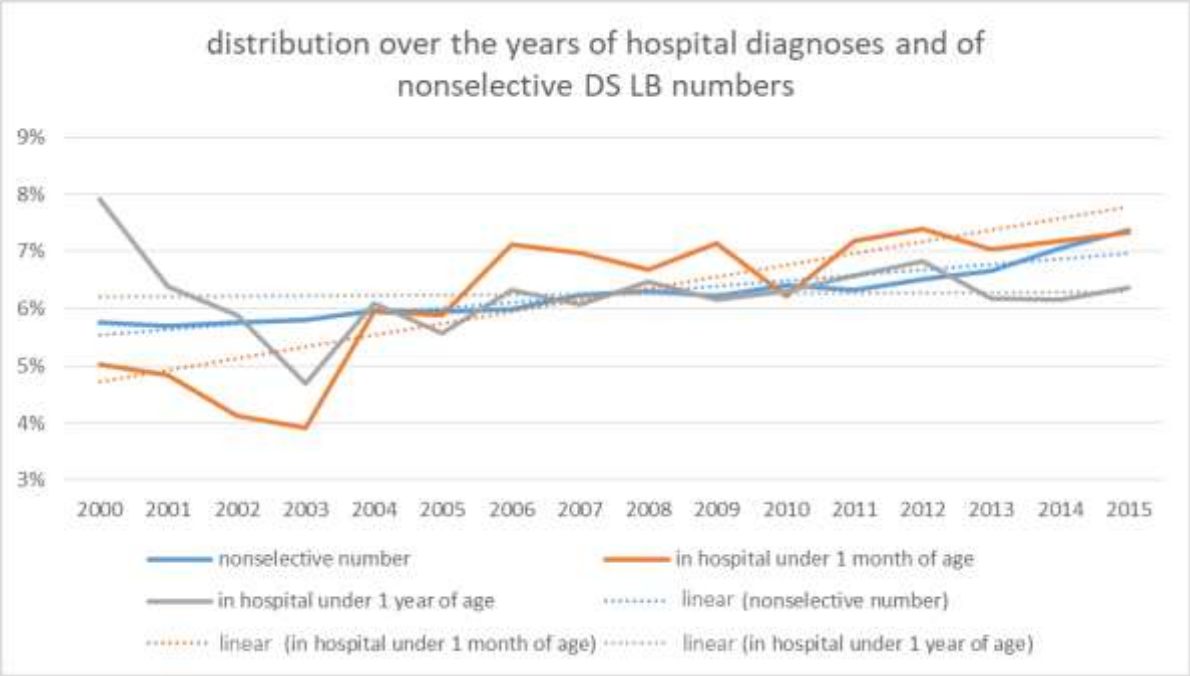


For 2000–2001, the reduction percentage for Germany, as a whole, was estimated around 50%. The graphs of Mainz and of Saxon-Anhalt suggest that in the period after 2000, reduction percentage was also around 50%. We have modeled reduction percentage after 2000 as such.

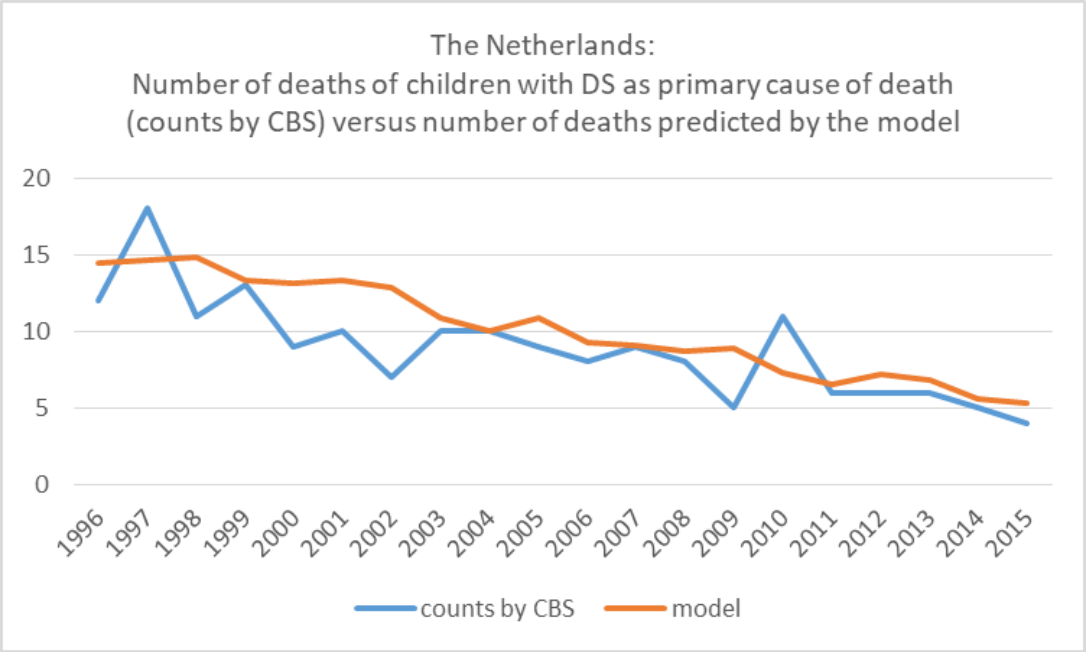
We would like to corroborate our model with national data. As a source, we found data from the German hospitals about the main diagnosis of children in hospital under 1 month of age, and under 1 year of age, from 2000 onwards. Not every child with DS will be reported as having DS as the main diagnosis for being in hospital. For instance, if we compare the number registered by the hospitals for Saxon-Anhalt with data from EUROCAT for Saxon-Anhalt, it appears that in this region around a quarter of the live born children with DS were registered as being in the hospital under the main diagnosis DS in the first month. However, we assume that the percentage of young children with DS that were registered with DS (as the main diagnosis) of all young children with DS will remain more or less stable over time. So, the hospital data can be used for looking at trends in time.



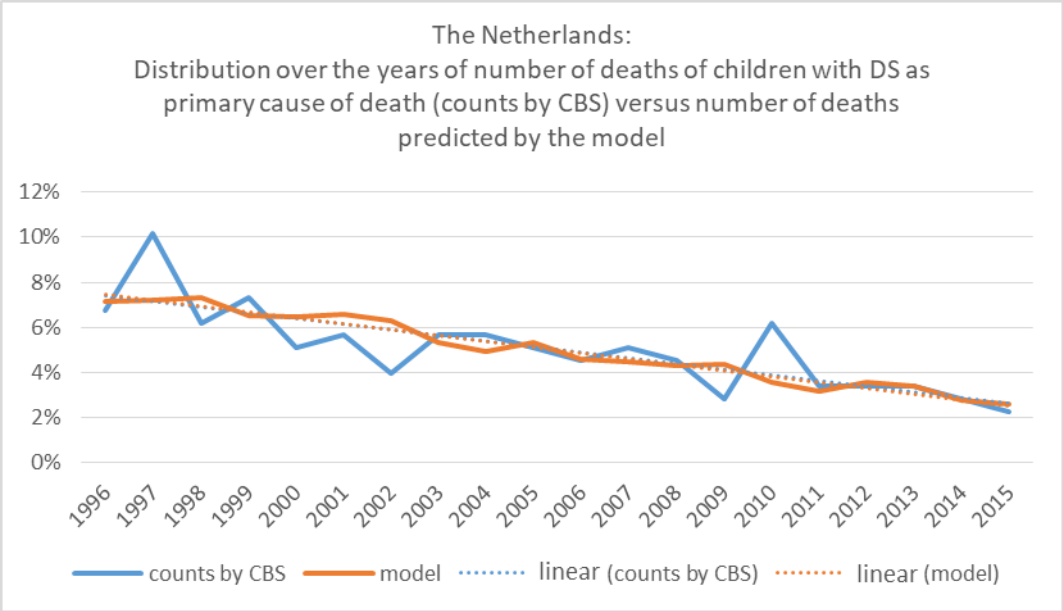
In the graph above, we see that both parameters show an increase between 2000–2015. This actually is in line with the development in nonselective numbers of DS, which also show a similar increase in this time period. To make the comparison easier to grasp visually, in the graph below, we have defined the total number of diagnoses in the period 2000–2015 in the hospital under 1 month of age at 100%, and then have calculated which is the distribution over the separate years as percentage of this baseline. We did similarly for diagnoses under 1 year of age, and for our estimates of nonselective numbers of LBs of children with DS. If the increase in numbers of diagnoses is similar in magnitude as the increase in nonselective numbers of LBs of children with DS, this implies that there were no changes in reduction percentage in the period under observation. The Figure below suggests that this is more or less the case. It implies that reduction percentage will have been similar to the value around 2000, that is around 50% in the period 2000-2015.



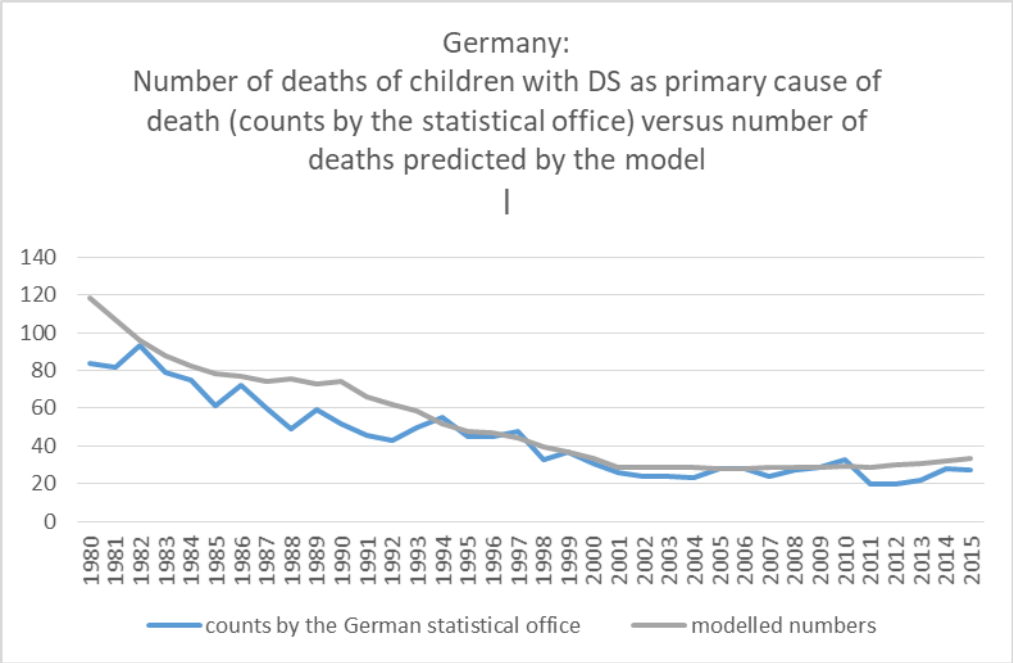
For a final check, we used data on the number of deaths with DS reported as the primary cause of death under 1 year of age and compared these with our model predictions for the same measure. To check whether this is a valid approach, we started by looking at the Netherlands, as valid national LB numbers for DS are known. CBS, the Dutch national statistical office, has data on DS as primary cause of death under 1 year of age from 1998 onwards. In the Figure below, we see the same trend in time in both variables.

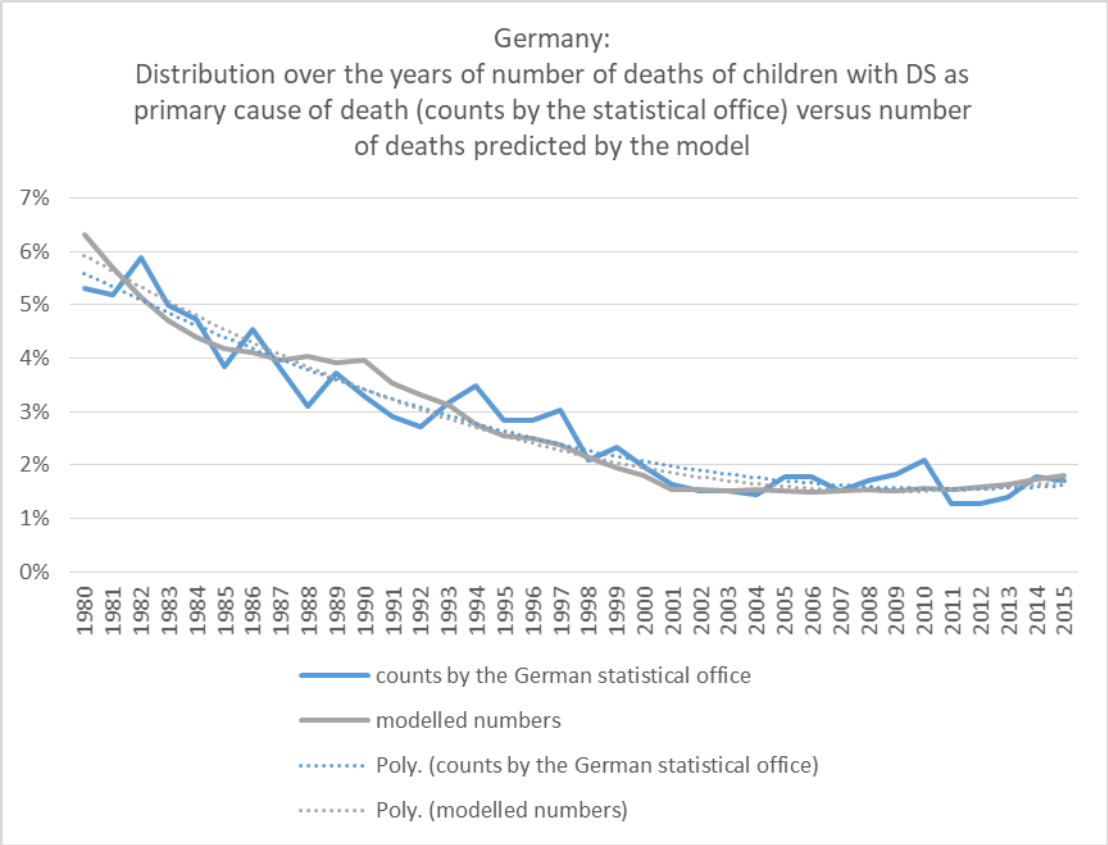


Not all young children with DS who are deceased will be assigned "DS" as primary cause of death on their death certificates. In the period under observation, in the Netherlands, the numbers counted are 89% of the numbers predicted. To make the trends in time easier to grasp, we defined the total number counted by CBS in the period 1996–2015 as 100%, and we then looked at the distribution over the separate years. We did the same for the model predictions. The Figure below shows a very good match.



For Germany between 1980–2015, we followed the same procedure. Around 85% of deaths of children with DS under 1 year of age (as modelled) were registered in the counts by the German statistical office, more or less similar to the Dutch situation (89%). We plotted the data in the Figures below. We consider the fit in the graphs between counts and predictions good enough.





Luxembourg

We have not found data on LBs of children with DS in Luxembourg. As a best approximation, we have modeled reduction percentage by averaging the reduction percentages in neighboring countries (France, Germany, and Belgium).

Netherlands

For 1986–2015, reliable estimates of national DS LB prevalence on the basis of data from the cytogenetic centers are available. For the period 2001–2015, we have full national data; for the

period 1986–2000, the data cover 50% of all Dutch births in 1986–1987, 63% in 1988–1990, 68% in 1991, increasing to 97% in 2000. For 1981–1985, data from EUROCAT for Northern Netherlands could be applied without correction, as for the period 1986–1990, estimates on basis of EUROCAT or on basis of the cytogenetic centers were highly similar. For the different years between 1976–1984, an estimation of the reduction by elective terminations was made on basis of the percentage of women (of 38+ years of age) that participated in the screening for DS (with amniocentesis or CVS) on basis of the maternal age criterion (38+ for these years). The estimated reduction of around 5% in 1975–1979 was projected linearly backward in time to 0.5% for 1965–1970.

Switzerland

For Switzerland, between 2003–2014, full counts of livebirths of children with Down syndrome were available from the Federal Statistical Office. For earlier years, we pooled data from EUROCAT for Vaud (available from 1989 onwards) with published data from the Eastern half of Switzerland for 1980–1996 (see S1D). These data cover around 56% of all births in Switzerland for 1980–1984, 58% for 1985–1989, 63% for 1990–1994, 33% for 1995–1999, and 10% for 2000–2002. For 2000–2002, only data from Vaud (EUROCAT) were available. A comparison of estimates of LBs of children with DS on basis of the EUROCAT data for 2003–2005 with the full counts from the Federal Statistical Office for 2003–2005 shows that these are highly similar (with a difference of around 7%).

Northern Europe

Denmark

Full information on DS prenatal and postnatal diagnoses, and LBs with DS are available (in Danish) for 1970–2017 from the Aarhus University Hospital. See S1D.

Estonia

For the period 1990–2005, full information on the number of LBs of children with DS is available in Reimand (2006) and for the period 2000–2014 in Lokko (2016). For 1990–2015, the WHO Regional Office for Europe (at https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births/) reports these numbers, too; however, the numbers reported are incomplete before 2000. The numbers of LBs of children with DS for 2000–2014 reported by the WHO are equal to the numbers reported by Lokko (2016). So, we expect the number for 2015, only reported by the WHO, to be correct, too. The number of nonselective LBs of children with DS for the period 1990–1992 equals the number of actual LBs for the same period. Thus, we assumed that reduction as a result of DS-related elective terminations was also zero for the period before 1990.

Finland

Finland has collected national data on births of children with DS from 1974 onwards. However, the way these data were collected has been revised in 1986 and again in 1993. According to THL (National Institute for Welfare and Health), the data from 1993 onwards are complete and accurate. From 1993–2011, these are reported by EUROCAT, divided into LBs, elective terminations, and natural losses. In the reports of THL, LBs and natural loss are pooled. From the EUROCAT data, we estimated that of the pooled numbers of LBs and natural loss, 95% were LBs. We have corrected the 2012–2014 data from the THL-reports to exclude this estimated 5% natural loss. The 2015-value for LB prevalence was estimated by projecting the reduction in LB prevalence in the period 2012–2014 forward on the estimate of the nonselective prevalence in 2015.

Data for the period 1986–1992 might be less accurate according to THL. However, THL states that the 1986–1992 data of the Register are being complemented by congenital anomaly data drawn from other registers. From 1986 onwards, data on elective terminations were collected, too. We checked

ascertainment by adding 0.73 of the number of elective terminations (to correct for natural loss that would have occurred in absence of terminations) to the number of LBs reported, and we compared these numbers to the estimates of nonselective numbers based on maternal age. For the period under observation, the first estimate was 11% higher than the second, suggesting there was no underascertainment.

The data from THL before 1986 appear to have considerable underascertainment. If these data were correct, it would suggest that reduction percentage was much higher in the late 1970's and early 1980s than later on (for instance around 66% in 1974 and 47% in 1985, compared to 21% for 1986–1988), estimated by comparing with the nonselective prevalence estimates). This doesn't seem logical. As such, for the period before 1986, we have linearly extrapolated reduction percentage backwards in time from 21% in 1985 (based on the THL data for 1986–1988) to 0% in 1967.

Iceland

Full information on LBs of children with DS for 1985–2017 is available from the State Diagnostic and Counselling Centre (see S1D). However, we suspect underascertainment in the early years of the register, as the reduction percentage estimate for 1985–1989 is much higher (51%) than for 1990–1994 (23%), which is not too be expected. As such, we have decided to not use the data for the first five years. For the period before 1990, we have projected reduction percentage backwards in time from 23% in 1992 (average of 1990–1994) to 0% in 1967. As numbers of births are very small in Iceland, resulting in large random fluctuations by year, for the period after 1990, we have decided to not directly use the counts. Instead, we have worked with 5-year running averages of reduction percentage estimates. That is, we have summed the counts for 1990–1994 and compared these with nonselective numbers for the same period to estimate reduction percentage as of 1992. Subsequently, we followed the same procedure for 1991–1995 (as an estimate for 1993), continuing to 2013–2017 (as an estimate for 2015). The reduction percentages were projected onto the nonselective numbers to estimate actual live birth prevalence.

Ireland

We used pooled EUROCAT data from 4 different regions of Ireland. For the period 1980–2015, the data covered on average 49% of the general births in Ireland, varying between around 40% to 65% for the different 5-year periods. Comparing the estimates of actual live birth prevalence with the nonselective prevalence shows that that the reduction percentage was around zero in the 1990s. As termination of pregnancy has been illegal in Ireland until very recently, reduction percentage is to be expected to be around zero. However, small numbers of expectant couples might travel to the UK for prenatal screening, and some couples expecting a child with DS might choose to do an elective termination in the UK. Reduction percentage for the 1980s, based on comparing EUROCAT counts with estimates of nonselective prevalence, suggest a reduction of around 5–7%. However, as the reduction was zero in the 1990s, we think it is more logical to assume a zero reduction for the 1980s, too. The discrepancy between the estimates of actual and nonselective prevalence might derive from regional differences inside Ireland, from underascertainment in the counts, and/or from uncertainty in estimating nonselective prevalence in relative small populations. For recent years (after 2000), the estimated reduction percentage is around 8–10%, which we have used in our modeling, assuming this is possible as some Irish pregnancies might be electively terminated in the UK.

Latvia

For 1990–2000, the WHO Regional Office for Europe (https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births/) reports the numbers of LBs of children with DS in Latvia. For 2000–2015, the numbers of LBs plus SBs is reported. We corrected for these by assuming that 95% of the reported

births (LBs plus SBs) were LBs (see also the section on Finland). In comparing the number of nonselective births of children with DS with the number of reported live births, it appears that the reduction as a result of DS-related elective terminations was around zero in the early 1990s. We assumed that this has also been the case before 1990.

Lithuania

The number of LBs of children with DS is reported by the WHO Regional Office for Europe for 1992–2015. It appears that the reduction as a result of DS-related elective terminations was around zero in the period 1992–1995. We assumed that this has also been the case before 1992.

Norway

Statistics Norway has information on the number of registered LBs with DS from 1967 onwards. However, in the Medical Birth Registry of Norway (MBRN), in the early years, there was considerable underascertainment. Bjerkedal & Kristensen (2007) conclude on basis of comparing DS in different registries, that on average about 72%of the live born children with DS were registered in MBRN in the period 1967–1976. In our estimations, we corrected The MBRN data for 1967–1976 for these missing cases. However, the corrected counts in the first five years of the register still appear to be too low to be considered reliable. If we compare with the nonselective estimates, reduction percentage in the period 1972–1976 was 3%, which is in line with what can be expected. However, in the period 1967–1971, if the corrected counts were accurate, this would have been 21%, which is highly improbable. Therefore, we have decided not to use the data from 1967–1972. For the period before 1974, we have linearly extrapolated reduction percentage backwards in time from 3% in 1974 (average for 1972–1976) to 0% in 1967.

We don't know if there was considerable underascertainment in later years. However, according to Klungsøyr et al. (2010), the data collection for the MBRN has been improved after a revision in 1999. Klungsøyr et al. examined the MBRN data for 2001–2005, by comparison with data of the cytogenetic laboratories, which can be considered to be reliable and complete. The MBDN missed 42 LBs that were reported by the cytogenetic laboratories, however the MBRN contained also 36 false positives. Therefore, the overall number was almost similar to the number on basis of the cytogenetic laboratories.

If the data of the MBRN for 1976–1998 were complete, this leads to an estimation of reduction percentage that is higher for the early 1990s (42% for 1991–1995) than for the early 2000s (33% for 2001–2005), which we think is unlikely and indicates underascertainment in the earlier data. As an alternative, for the period before 1976–1998, we have linearly extrapolated reduction percentage backwards in time from 32% in 1998 (average for 1999–2003) to 3% in 1974. The numbers in the MBRN are on average 87% of these numbers constructed on basis of this extrapolation, and it is not unlikely that the MBRN had an underascertainment of this magnitude in the period under observation. For our modelling, we have used the extrapolated number for the period 1976–1998.

Sweden

The most comprehensive data can be found in the research from Englund et al. (doi: 10.1002/ajmg.a.35706) and in the Annual report from the Swedish Birth Defects Registry 2016. Englund et al. published data on LBs of children with DS for the period 1974–2003, based on counts in the Swedish Medical Birth Register, and the Swedish Birth Defects Register, including the Swedish Cytogenetic Register. For 1973–2016, there are national counts available in the Annual report from the Swedish Birth Defects Registry 2016, based on counts in the Surveillance Register of Birth Defects (FoK), the Medical Birth Register (MFR), and the patient register (PAR). The counts of births in the Annual Report probably contain a small percentage of natural loss (miscarriages and SBs). We

corrected for these by assuming that 95% of the reported births were LBs (see the section on Finland).

For the period 1974–1997, numbers of LBs with DS in Englund et al. are 16% higher than the counts reported in the Annual Report (or even 22% higher if we correct the data from the Annual Report for natural loss first). As this indicates that there is some underascertainment in the Annual Report, we have decided to use the data from Englund et al. for 1974–1997. However, for 1974–1977, the reported numbers are slightly higher than the expected numbers on basis of our estimations of nonselective numbers. Therefore, we have modelled the reduction percentage to be zero before 1978.

For the period 1998–2003, numbers based on the Annual Report (corrected for natural loss), and the numbers of LBs reported by Englund are almost identical (with on average only 3% difference). We have decided to use the data of Englund et al. for this period. Finally, for the period 2004–2015, we used the data from the Annual Report (corrected for natural losses).

United Kingdom

For England/Wales (1989–2013), Scotland (1991–2011), and Northern Ireland (2007–2016), reliable and complete national data were available (see S1B). Reduction percentages for England/Wales versus Scotland slightly differed in the period 1991–2011. We plotted the reduction percentage for the data from England/Wales and Scotland taken together against the reduction percentage based on NDSCR (for England/Wales only) for this period. With a linear regression, the first can be predicted on basis of the second ($R^2 = 0.99$). We used this regression to predict the reduction percentage for England/Wales and Scotland combined for 1989–1990 and 2012–13 on basis of the reduction percentage as based on the NDSCR-report for 1989–1990, and for 2012–13 respectively. For the period 2014 and 2015, we used EUROCAT data to estimate LB prevalence in England/Wales and Scotland, as LB prevalence estimates based on EUROCAT data were very similar to these estimates based on NDSCR data in the period before 2014. We estimated LB prevalence in England/Wales and Scotland on basis of EUROCAT data for the period 1980–1988, too. For that period, EUROCAT actually only has data from Glasgow, however LB prevalence estimates based on the data from Glasgow for the period 1989–2000 were similar to estimates based on all UK EUROCAT registries taken together and to estimates on basis of NDSCR data.

For the period before 1989, we compared our estimates for England/Wales and Scotland combined with estimates found in the literature. Huether et al. (1996) had data on DS LB prevalence for a small Scottish area for the period 1978–1992. Their data were highly similar to these from the Glasgow area, the average live birth prevalence for 1980-1990 being less than 1% different. Cuckle et al. (1991) estimated the LB prevalence in England/Wales for 1974–1987 by subtracting 0.74 of the number of abortions registered as an abortion of a fetus with DS—that is, the 74% to correct for spontaneous losses that would have occurred absent elective terminations—from the nonselective prevalence estimated on basis of maternal ages. Their estimates of LB prevalence are slightly higher than ours. However, they assumed a 100% ascertainment of these abortions, which is highly improbable. Comparing the number of abortions of fetuses with DS as registered by the Office for National Statistics for the period 1989–1993 in England/Wales to this number reported by NDSCR reveals that ONS only registers about 54%. Reconstructing the live birth prevalence estimates, assuming an ascertainment of abortion of fetuses with DS of 54%, produces a prevalence for the 1980s similar to ours based on EUROCAT Glasgow. For the period 1980–1985, we estimated reduction percentage to be 26% in England/Wales and Scotland combined. We projected linearly backward in time to 0.5% for 1965–1970.

Northern Ireland had a much lower reduction percentage for 2007–2013 than in England/Wales (and Scotland) in the same period. We estimated the reduction percentage for Northern Ireland to be around 23% for the period 2010–2015 and projected linearly backward in time to 0.5% for 1965–1970.

Southern Europe

Albania

National data on LBs with DS are available for 2011-2018 from the Institute of Public Health (and were reported to us in email by D. Çanaku (see S1D)). Comparing reported numbers with nonselective estimates, reduction percentage turned out to be on average 34% in the period 2011-15, 43% for 2013-15, 29% for 2011-13, and even as low as 20% for 2011-12. We have assumed that in the period 2006-2010 reduction percentage will have been 20% on average, similar to what was reported for 2011-12. Before 1990, abortion was illegal in Albania (https://en.wikipedia.org/wiki/Abortion_in_Albania). We expect reduction percentage to be around zero before 1990. For the period 1990-2005, we have interpolated the reduction percentage.

Bosnia and Herzegovina

Data on LB-prevalence of DS and number of LBs with DS are available for 2005–2018 in Kurtovic-Kozaric et al. (2016). We have used these data for 2005 and onwards. According to Kurtovic-Kozaric et al., CVS and amniocentesis were introduced in Bosnia and Herzegovina as of 2008. Therefore, we assumed that the reduction percentage was around zero in the years before 2005.

Croatia

The EUROCAT data for 1983–2015 (combined with the data on Primorskogoranska for 1996–2005) cover, on average, 14% of the LBs in Croatia (see S1D). As Croatia is a small country, there inevitably will be random fluctuation in these numbers. In addition, Zagreb might be different from rural areas. The 2009–2012 data of Glivetic et al (2015) cover Croatia as a whole, but appear to be an under-ascertainment, as the number of people with DS alive in Croatia, as of 2018, from the years of birth 2009–2012, as reported by the Croatian Institute of Public Health (received in personal e-mail (August 21, 2019) from Dinka Vukovic of Croatia Down Syndrome Association), are much higher than the numbers of LBs reported by Glivetic for this same range of years. Therefore, as an alternative, we chose to construct the number of LBs on basis of the number of people with DS alive as reported by the Croatian Institute of Public Health.

To check for possible under-ascertainment, we have compared the data by year of birth of the Croatian Institute of Public Health as of 2018 with their data as of 2015.

Year of birth	A. Registered number alive in 2018	B. Number expected to be alive in 2015 based on 2018-registration combined with survival model	C. Registered number alive in 2015
2011–15	185	191	108
2006–10	237	240	224
2001–05	227	229	239
1996–00	232	235	243
1991–95	176	178	186
1986–90	131	133	135
1981–85	107	108	103
1976–80	105	107	106
1971–75	105	109	106

1966–70	50	54	51
1961–65	59	67	52
1956–60	23	29	29
1951–55	10	15	19
≤ 1950	3	5	6

In the Table, you find numbers of people with DS in Croatia as registered by the Croatian Institute of Public Health. Column A contains the numbers as registered in 2018. Column B is a projection of the numbers from Column A back in time to 2015 on the basis of modeled survival between 2015–2018. Column C is the number as registered by the Croatian Institute of Public Health as of 2015.

We expect for 2015–18 that survival in Croatia is not extraordinary unfavorable—and would be comparable to Western European countries—as 1-year survival in the general population of Croatia is relatively low and has been in line with Western European countries from 2000 onwards. This suggests a good health care system is in place during this period.

For most years of birth, the numbers in Column C more or less equals the numbers in Column B. If the number in 2015 (Column C) is larger than the number in Column B, then probably survival between 2015 and 2018 was a bit less favorable than modeled. If the number in 2015 (Column C) is smaller than the number in Column B, especially if the number in Column C is also smaller than the number in Column A, then there was an under-registration in 2015. This is clearly the case for the years of birth 2011–15 (only 57% of persons in Column B are registered in Column C). For the older age groups, there is only some indication of undercounting as of 2015, especially for the years of birth 2006–2010 (93% of Column B seems to be registered in Column C), and for 1961–65 (78%).

As 1-year survival in the general Croatian population is comparable to Western European values, we assumed that we could use a model of survival for children with DS that was in line with the Western European situation to construct the probable number of LBs of children with DS for the years of birth 2000 onwards. As the registered data as of 2015 for children aged 0–5 clearly are subject to under-ascertainment (i.e., much more were registered in 2018), the data for children that are under five years of age in 2018 probably are subject to under-ascertainment, too. However, the 2018-data for the years of birth 2000–2013 can be considered to be fairly complete. In the Table below, we have estimated the number of LBs that are in line with the numbers alive from these years of birth, as registered in 2018, assuming a Western European type of survival for children with DS in Croatia from 2000 onwards.

Year of birth	**D. Number of registered people with DS alive in 2018**	**E. Estimated number of LBs based on 2018-registration combined with survival model**
2000	43	54
2001	40	48
2002	56	65
2003	45	50
2004	38	42
2005	48	53
2006	52	57
2007	51	56

2008	50	55
2009	50	55
2010	34	37
2011	43	47
2012	48	52
2013	48	52

The corresponding reduction percentage for 2011–13 is 37%. We assumed that this reduction percentage would also apply to 2014 and 2015. If, instead, we would have used data on actual live birth prevalence from EUROCAT for these two years, the corresponding estimate of reduction percentage would have been very similar at 38%. For the period 2000–2004, the corresponding reduction percentage is 21%. Based on EUROCAT data on actual prevalence (combined with the data on Primorskogoranska for 1996–2005), this would be 22% for 1996–2000, and 21% for 1991–1995. Before 1990, EUROCAT-based actual prevalence exceeds our estimates for nonselective prevalence. Therefore, we have assumed that before 1990 reduction percentage will have been around zero. We applied these estimates of reduction percentage to the nonselective numbers before the year of birth 2000 to model actual LBs of children with DS.

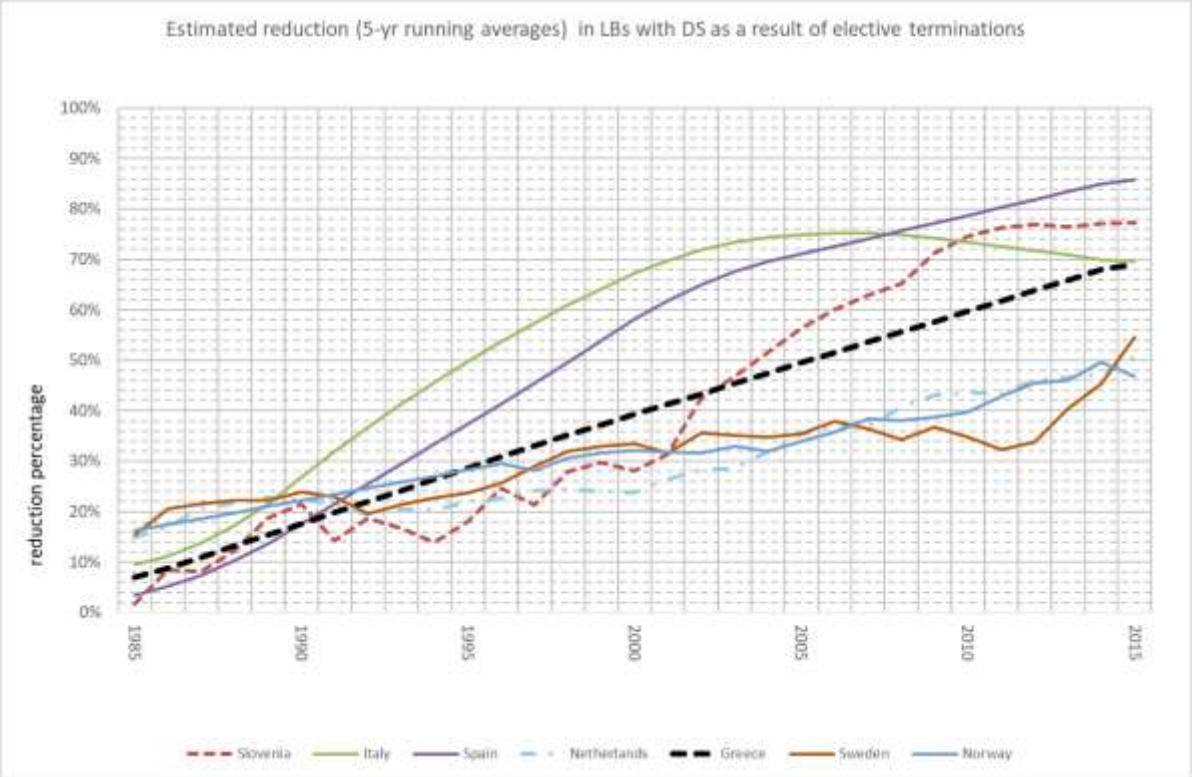
Greece

There are limited data from Greece. We found the number of invasive prenatal procedures in 1976, 1980, 1984, and 1996—that is, 5, 450, 1,000 and 6,500, respectively. The next step was to estimate how many births of children with DS were prevented as a result of these procedures, followed by an elective abortion. To model this, we made use of Dutch data from WPDT-reports (Annual reports of the Working Party Prenatal Diagnosis and Therapy)—which are complete—on the total number of amniocenteses and the total number of elective terminations of fetuses with DS after amniocentesis along with the total number of CVS and the total number of elective terminations of fetuses with DS after CVS by year, in the Netherlands for the period 1991–2003. (For the years before 1991, we applied the average of the Dutch data for 1991–1993.) The relation between the number of amniocenteses/CVS and the number of children with DS that were aborted changes in time, as advancements in technical characteristics of screening allow a more precise assessment of risk. We assume that this development is similar in the Netherlands and Greece, and we assume that continuing a pregnancy after a prenatal diagnosis in this period was similarly rare in both the Netherlands (WPDT-reports) and Greece. The relation between total number of invasive procedures and number of DS-related terminations in the Netherlands by year (using running 3-year averages) was projected on the number of invasive procedures in Greece. The estimated number of children with DS not born as result of screening in Greece was around zero in 1976, 3 in 1980, 7 in 1984, and 45 in 1995, which corresponds with a reduction percentage of zero in 1976, 2% in 1980, 4% in 1984, and 29% in 1995, respectively. For 1976–1995, we interpolated in-between values.

The 29% in 1995 is comparable with the situation in the same year in the Netherlands (26%), Sweden (28%), and Norway (28%), but much lower than in some of the other South European countries, like Italy (50%), or Portugal (57%). How has the Greek situation developed, though, after 1995? In general, the countries that had a relatively low reduction percentage in 1995 also had a relatively low, but increased, percentage in 2015. The Netherlands went from 26% to 51%, Sweden from 28% to 55%, Norway from 28% to 48%, in contrast to Italy, which went from 50% to 70% and Portugal from 57% to 80%. If Greece developed similarly to the Netherlands, Norway, and Sweden, one would expect a reduction percentage of around 54% in 2015. However, it was not always the case that a relatively low reduction percentage in 1995 corresponded to a relatively low reduction in 2015.

Slovenia was this exception, going up from a relatively low 18% in 1992–1994 to an estimated 77% in 2015.

We have found some extra indirect information on Greece. Ettore (2018) studied the attitudes of physicians, midwives, press, and pregnant women toward prenatal screening in Greece, compared to other European countries (the Netherlands, Finland, England) in the period 1996–1999. In Greece, physicians, midwives, professional and layman press, and pregnant women were welcoming of prenatal screening. The vast majority of midwives in Greece (and in Finland and England, but not in the Netherlands) were proponents of universal maternal serum screening. Samakouri et al. (2018) looked at attitudes, perceptions, and ideas relating to prenatal diagnostics of Greek pregnant women (compared to other European countries) in the period 2005–2008. These researchers conclude that—much stronger than in some other European countries (England, Sweden, Germany, Italy)—Greek pregnant women comply with their doctor's recommendations, which, in Greece, is very directive. Earlier, we have seen in Ettore et al. that physicians and midwives were welcoming about prenatal screening, so we would expect that they recommend such screening and that Greek women would follow these recommendation. Finally, Gourounti & Sandall (2008) report that in a hospital in Athens 96% of women just before antenatal screening had a welcoming attitude toward screening (though only 45% had a good level of knowledge concerning the screening process for DS). As attitudes towards prenatal screening for DS appear to be welcoming among Greek pregnant women, physicians, and midwives, we would expect that uptake of screening, and thus reduction percentage, would be relatively high. As such, we took the Italian value of 70% in 2015 (which is the lowest value among the Southern European countries of Italy, Spain, and Portugal) as the best and safest approximation to project onto Greece. We extrapolated the values between 1995 (29%) and 2015 (70%). The result is depicted in the Figure below.



Italy

We used pooled EUROCAT data from 5 different regions. For the period 1980–2014, the data cover on average 18% of the general births in Italy, with 9% for 1980–1984, 13% for 1985–1989, 20% for 1990–1994, 30% for 1995–1999, 32% for 2000–2004, 13% for 2005–2009, and 13% for 2010–2014. From 2005 onwards, data were available for two regions only (Emilia Romagna and Tuscany). For the period 1995–2004, estimates of actual live birth prevalence for DS based on these two regions were on average 17% lower than estimates based on all available data. We have assumed this to be the case for the period after 2004 too. To avoid underestimation, we have corrected the estimates for 2005–2009 and 2010–2014 accordingly by multiplying the initial estimates with 1.17. Average reduction percentage for 2005–2009 was estimated at 79% initially and at 76% after correction. For 2010–2014, these values were 76% and 72%, respectively.

Malta

We have assumed that reduction percentage is zero in Malta, as terminations are completely illegal. This is corroborated by the data of EUROCAT, which are available for Malta from 1986 onwards. In the period 1986–1995, EUROCAT counted 95 LBs of children with DS; our model predicts 95. For 1996–2005, these numbers are 78 and 72 (8% difference), respectively. For 2006–2015, 77 and 77. However, as numbers of births are very small in Malta, this can result in large random fluctuations of actual number of LBs with DS by year. Therefore, we decided not to use the direct counts of EUROCAT in subsequent modeling of population prevalence, but, instead, we built upon nonselective numbers.

Montenegro

There is very little information on the situation in Montenegro. We found a report of the OECD (2006) that states that at that time there was no possibility for prenatal detection of disorders in Montenegro. The Government of Montenegro (2009) reported on their application for membership of the European Union that as a measure to decrease infant mortality (which, according to the report, was relatively high in 2007) a Prenatal Diagnosis Committee had been established, which helps to routinely refer all pregnant women older than 35 and younger than 18 to the Council for Prenatal Diagnostics, which approves and runs invasive diagnostics. As such, this appears to be a fairly recent development. We assumed that reduction percentage before 2009 will have been around zero. We estimated that in the period 2010–2015, in absence of elective terminations, around 55% of the births of children with DS would have been to women of 35 years and older and women under 20 years combined. If 90% of these women were to have had prenatal diagnostics followed by an elective termination, reduction percentage would be 50%. Such rapid increase is not impossible; for instance, in Bosnia and Herzegovina the reduction percentage rose from around zero before 2005 to an estimated 49% in 2011–2015.

North Macedonia

For North Macedonia-, there is extremely little information on the LB-prevalence of DS, and only some indirect data exist. According to Sukarova-Angelovska & Petlichkovski (2018), amniocentesis was introduced in North Macedonia in 1976, and chorionic biopsy in 1990. Zisovska & Lazovska (2006) reported 24 LBs of children with DS out of 19,920 newborns, corresponding to a LB prevalence of 12 per 10,000. We estimated nonselective prevalence for the period 2005–2010 at 13.3 per 10,000. An actual prevalence of 12 per 10,000 suggests a reduction percentage of only 10%. However, the women in the study had given birth in a hospital in Skopje, and maternal age in Skopje might be higher than in North Macedonia, as a whole. Interestingly, Zisovska & Lazovska also reported the incidence by age group. They found 1 in 1,680 in mothers <25 years of age, 1 in 1190 in 24–35 years of age, 1 in 430 in 35–40, and 1 in 140 in 40 years and over. We applied these chances to

the numbers of mothers in North Macedonia by age group in the period 2005–2010, as estimated by the World Population Prospects of the United Nations. This leads to an estimation of 105 LBs of children with DS in North Macedonia during this period. Our estimate of the nonselective number was 152 children. The corresponding reduction percentage, for all ages combined, is 31% (14% for <25; 21% for 24–35; 51% for 35–40, and 57% for 40+). We assumed that this 31% reduction would apply to the North Macedonian situation in 2005. We have extrapolated linearly backwards in time to 0% reduction in 1976, and we have extrapolated forward assuming the same annual increase between 2005 and 2015 as in the preceding years. This produces a reduction percentage of 40% for 2010–2015 (and a development in time that is more or less similar to Croatia). If, alternatively we assumed there would be no increase at all in usage of prenatal diagnostics in one and the same age group and we applied the reduction percentages by age group (as presented above) to the estimated numbers of nonselective LBs of children with DS by age group in the period 2010–2015, the corresponding reduction percentage for all age groups together would be 34% for this period. As we think that some increase of usage is more logical, we will use the first estimate of 40% instead.

Portugal

From 1990 onwards, EUROCAT data are available from Southern Portugal. For the period 1990–2015, the data cover on average 15% of the general births in Portugal, with 8% for 1990–1994, 15% for 1995–1999, 17% for 2000–2004, 19% for 2005–2009, and 20% for 2010–2014. In addition, national numbers of LBs with DS are available for 2000 and 2001 from the Centro De Estudos E Registo De Anomalias Congénitas. We have used these national data for 2000 and 2001. Our estimation on the basis of EUROCAT was only 3% lower for these two years, which implies that the EUROCAT data seem to be representative for Portugal. Abortion was completely illegal in Portugal until 1984 (Vilar, 2002, DOI: 10.1016/S0968-8080(02)00025-3.) We have assumed that that reduction percentage was around zero for 1980–1984. For 1985–1989, we have interpolated.

Serbia

Dimitrijevic et al. (2013) reported 15 LBs of children with DS between January 2007 and December 2011 in 10,822 LBs in Kragujevac. This corresponds to a LB prevalence of 13.9 per 10,000 LBs. Nonselective prevalence for Serbia as a whole (including Kosovo, but maternal age distribution in Kosovo is highly similar to that in Serbia) was modeled at 16.6 per 10,000 LBs. Reduction percentage for 2007–2011 would be 17% based on comparing the LB prevalence in Kragujevac with our estimate of Serbian nonselective prevalence.

Milićević et al. (2019) report 106 prenatal diagnoses of children with DS in the period 2004–2017 in Niš. The area covered by the Clinical Center of Niš as a reference health center includes territories of Southern and Eastern Serbia with a total population of about two million inhabitants. If nonselective prevalence and birth rates in these areas are similar to Serbia as a whole, our model would predict 523 LBs of children with DS during this period. The number of 106 prenatal diagnoses—assuming none of these were LBs and correcting for natural loss that would have occurred absent elective abortions—corresponds to around 77 LBs prevented. That implies a 15% reduction rate for this period. However, this might be an underestimation of the reduction, as we don't know if all pregnant women in the area who make use of prenatal diagnostics go to the Clinical Centre in Niš.

DS LB prevalence for 2006—2015 is reported by the WHO Regional Office for Europe. Data are based on birth reports of children diagnosed (ICD10: Q90) after birth and before discharge from the newborn from the maternity ward. The data appear to be far from complete. For 2007–2011, the WHO-data would suggest a LB-prevalence of 3.9 per 10,000 LBs, whereas the LB-prevalence estimate for Kragujevac was 13.9 per 10,000 LBs, which is 3.5 times as high. We have multiplied the WHO-data with 3.5 and looked at the resulting estimates of LB-prevalence in order to check whether these

numbers show a trend in time. We divided these estimates by our modeled nonselective DS prevalences to estimate the corresponding reduction percentages. We calculated 5-year running averages and estimated the best fitting linear equation predicting these by year of birth. This yielded a reduction percentage increasing from 0% in 2003 to 40% in 2015. Estimated reduction percentage for 2007–2011 is 17% (like we had estimated on the basis of the data from Kragujevac). Estimated reduction percentage for 2004–2017 would be 23%, which is higher than the 15% we had estimated for Southern and Eastern Serbia for the same period. However, as stated above, the 15% might be an underestimation. For our modeling of Serbia (excluding Kosovo), we have used our estimate of reduction percentage increasing from 0% in 2003 to 40% in 2015.

For Kosovo, Kolgeci et al. (2013) reported cytogenetic diagnoses of DS in LBs for the period 2000–2010. These data seem to be incomplete. We could find data on maternal age in Kosovo through the Kosovo Agency of Statistics (http://ask.rks-gov.net/en/ retrieved September 21, 2019) for 2010 onwards. On basis of these data, we estimated that there would have been 59 LBs of children with DS in Kosovo, absent of elective terminations in 2010. Kolgeci et al. report only 26 for 2010, suggesting a reduction percentage of 56%. However, Kolgeci et al. explain that there are no prenatal screening tests (ultrasound and biochemical screening) or prenatal diagnostic tests (chorionic villus sampling, amniocentesis, cordocentesis) available in Kosovo. That makes a high reduction percentage extremely unlikely. The relatively low numbers of karyotyped children with DS might indicate that many children had not been karyotyped at all. In absence of prenatal screening and testing, we would expect a reduction of around zero for Kosovo. The trend in time for LB-prevalence in Kosovo based on the counts of Kolgeci et al. corresponds to the trend in our nonselective prevalence estimates for Serbia (including Kosovo), both showing a comparable slight increase from 2000 to 2010, which suggests that in Kosovo there has not been an increase of reduction percentage in this period. For our modeling, we will assume that in Kosovo the reduction has been zero.

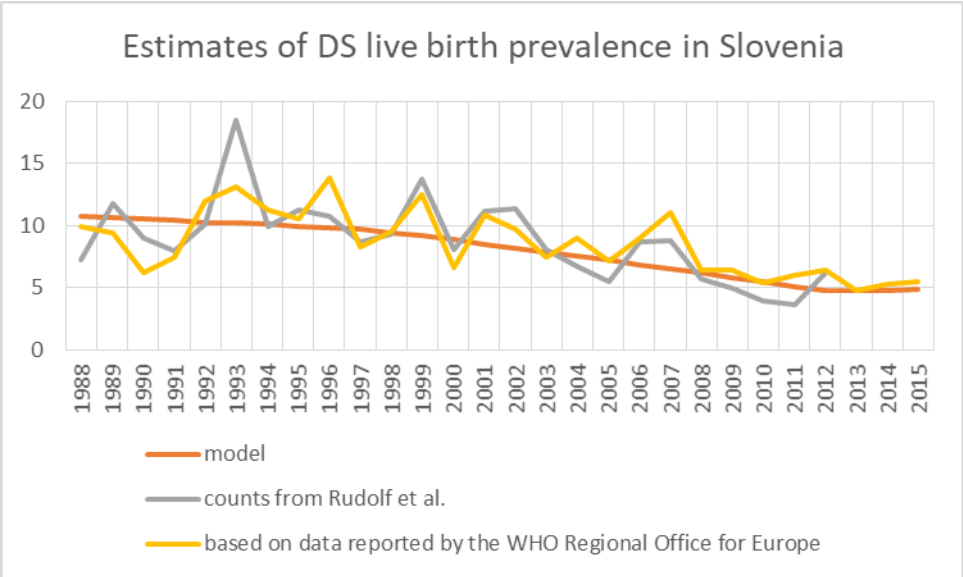
Slovenia

National data on number of prenatal and postnatal diagnoses of Down syndrome are available in Rudolf et al. (2017). To construct the number of LBs, we assumed that 5% of prenatal diagnoses were a LB, and we assumed that 5% of the postnatal diagnoses were still births. We compared these estimates of LBs with the nonselective numbers to construct reduction percentages by period. We used the data for 1981–1984 to estimate reduction in 1980–1984; 1985–1989 for 1985–1989, 1990–1994 for 1990–1994, etc. As the most recent available data were from 2012, we used the data for 2010–2012 to estimate reduction for 2010–2014.

However, the estimate of reduction percentage for 1980–1984 would be 36%, which is highly improbable, as the reduction percentage for 1985–1989 and for 1990–1994 are much lower—i.e., 2% and 15%, respectively. In addition, in the period 1980–1984, the percentage of registered children karyotyped prenatally was only 4%, and the total number of cases was far below the number expected on the basis of maternal age. The register, which is based on data from the cytogenetic laboratories, seems to under-ascertain LBs of children with DS before 1985, probably because in that period not all babies were karyotyped. Therefore, we have assumed that reduction percentage in that period was (at most) 2%, which is the estimate for 1985–1989. According to Rudolf et al., the first amniocentesis in Slovenia was performed in 1981 and the first CVS in 1985. We assume that reduction was zero before 1980.

In addition, DS birth prevalence for 1988–2015 is reported at https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births based on data from the National Institute of Public Health, Slovenia (NIJZ). Whether SBs or TOPs are included was not specified. However, for the overlapping years of birth 1988–2012,

these data do correlate with the data from Rudolf et al. (R^2=0.63) and show the same development over time (see Figure below). The development in the data from the National Institute of Public Health after 2012 is in accordance with out modeled estimates.



Finally, in estimating the birth and population prevalence of DS, we have used our estimates on the basis of the national data from Rudolf et al. for 1986–2012 by year of birth (grey line in the Figure above) and relied on our modeled estimates on the basis of an average 5-year reduction percentages for the years before 1986 and after 2012 (orange line).

Spain

We used pooled EUROCAT data from 4 different geographical areas, combined with EUROCAT data from the national Spain Hospital Network. For the period 1980–2014, the data cover on average 26% of the general births in Spain, with 12% for 1980–1984, 13% for 1985–1989, 30% for 1990–1994, 36% for 1995–1999, 34% for 2000–2004, 34% for 2005–2009, and 26% for 2010–2014. In the period 1980–1989, data are available only from the Spain Hospital Network. However, for the period 1990–1994, the LB prevalence estimate based on the Spain Hospital Network is highly similar to an estimate based on the three available EUROCAT regions in this period (Asturias, Barcelona, Basque Country). The difference was less than 10%, and for the period 1995–1999, the difference was even less than 3%. As such, the data for 1980–1989 from the Hospital Network might be representative for Spain, as a whole. However, using these data to estimate reduction percentage leads to a value of 6% reduction for 1985–1989 and to a value of 14% for 1980–1984. This last percentage of 14% is highly improbable, as abortion was illegal in Spain up to July 5, 1985, with the passing of the Organic Law 9/1985 (https://en.wikipedia.org/wiki/Abortion_in_Spain). We have therefore assumed that reduction percentage was around zero for 1980–1984, instead.

Eastern Europe

Belarus

Full data on LB prevalence of children with DS in Belarus were collected and reported for 1981–2001 by the Belarus National Registry, clustered for the years of birth 1981–1986, and from 1987 onwards by year of birth. We have compared actual LB prevalence for 1987–2001 with our estimates of nonselective LB prevalence to estimate reduction percentage. Reduction was 0% for 1987–1989,

which makes sense as the first elective terminations in this article date from 1992. Reduction percentage increases to 21% in 1997–2001. For the period 1997–2015, we have the number of children under 1 year of age with DS as a morbidity as reported by the WHO Regional Office for Europe. If we look at the overlapping 5 year period 1997–2001, it appears that the Belarus National Registry reports 1.8 times as many LBs of children with DS as reported by the WHO. We have assumed that the data by the WHO have the same magnitude of undercounting in the years after 2001 and have multiplied their estimates with 1.8. We have used these data to estimate the actual LB prevalence, and the corresponding reduction percentage, for the period 2001–2005, 2006–2010, and 2011–2015. For these three periods, estimated reduction percentage was 27%, 26%, and 46% respectively. In modeling for 1987–2001, we have used the actual LB prevalence reported by the Belarus National Registry. For the years after 2001, we have used the estimates of LB prevalence multiplied by 1.8 of the WHO.

Bulgaria

In Bulgaria, maternal biochemical screening test are implemented since 1996, and NIPT has been available since 2014 (Levkova et al., 2018). However, in the period 1996–1999, the net effect on LB prevalence was probably small. EUROCAT data for Sofia in the period 1996–1999 show an actual LB prevalence for DS of 11.5 per 10,000, which is 99% of our estimate of nonselective LB prevalence for the same period. Of course, it is possible that Sofia had higher maternal ages than Bulgaria, as a whole, which would make our estimate of reduction too low. However, in the EUROCAT data only 3 terminations are reported alongside 44 LBs, which suggests a reduction percentage of only ~5%. In contrast, in recent years, data suggest a relatively high reduction percentage in Bulgaria. Yankova & Savov (2014) report that there were 152 LBs of children with DS in Bulgaria in the period 2008–2012. We estimated a number of 578 nonselective births for the same period. Taken together, this suggests a reduction percentage of 74% for 2008–2012. The possibility of a high reduction percentage in recent years is corroborated by findings of Levkova et al. (2018). In a survey in 2018 among 500 randomly selected Bulgarian women with mean age 30.86 (from 18 to 47), around 70% of the respondents had chosen to do a biochemical screening during their current or previous pregnancy. In our modeling, on basis of the data above, we assumed a reduction percentage of 5% for the late 1990s and of 74% for 2008 and onwards. For 1999–2007, we interpolated. For the years preceding 1996, we have extrapolated linearly backwards in time to 0% in 1967.

Czech Republic

Data on LBs with DS (for the whole country) are available for 1961–2012. As Sípek et al. (2009) report that the first prenatal diagnosis in the Czech Republic was in 1980, we assumed a reduction percentage of 0% before 1980. For 1974–1999, we have used the data from the Clearinghouse Annual Report, and for 2000–2012, we used the data from EUROCAT, both sources covering all births in Czech Republic. For 2013–15, we assumed that the reduction percentage was similar to that in 2010–12.

Hungary

Data on LBs with DS (for the whole country) are available for 1974–2012. According to Czeizel (1988), a change of law in 1974 made medically indicated induced abortions possible under less restrictions; the number of medically indicated induced abortions increased significantly after 1973, and genetic counseling clinics were founded in 1976. The data from the Clearinghouse Annual Report (2014) for 1974–1980 appear to be in line with a relatively early implementation of prenatal diagnostic services. We have used the numbers of LBs with DS from the Clearinghouse Annual Report and from EUROCAT for 1974–2012. For 2013–15, we assumed that the reduction percentage was similar to that in 2010–12.

Poland

Data on LBs with DS are available for 1999–2015 through EUROCAT. For the period 1999–2015, the data cover on average 79% of the general births in Poland, with 39% for 1999–2000, 65% for 2001–2005, 88% for 2006–2010, and 98% for 2011–2015. Data before 1999 are not available, but reduction percentage was 1% for 1999–2001. We would expect that reduction percentage was as low before 1999 (in the 1990s). In 1990, after the end of Communist rule, Ordinance of 30 April 1990 made access to abortion more difficult (https://en.wikipedia.org/wiki/Abortion_in_Poland). Before 1990, we could find only data from South Poland (Pietryzyk & Majerska, 1987), which shows that actual LB prevalence of DS in this region was higher than our modeled nonselective prevalence for Poland in the mid-1980s. Therefore, we have assumed that reduction percentage was around zero before 1990.

Republic of Moldova

Barbova et al. (2014) report 359 LBs and 43 prenatal diagnoses of DS for 2005–2012, on the basis of the Register of congenital anomalies from the Republic of Moldova. After correcting for an estimated 27% natural loss (that would have occurred in the 43 prenatal cases in the absence of elective terminations), this yields an estimate of 390 children with DS that would have been born in the absence of elective terminations. Our modeled estimate for the number of nonselective births of children with DS in Moldovia for this period is 392; so it can be concluded that the register has complete data. For the period 2005–2012, we have used the number of LBs as reported by the Register. As the data from the Register seem to be complete, we have estimated reduction percentage for 2005–2012 by dividing the registered number of LBs of children with DS by the expected number [*registered number of LBs* + (0.73 x *the registered number of DS prenatal diagnoses*)]. We have plotted these estimates of reduction against the year of birth and fitted the corresponding linear equation to this plot. This produces estimates of reduction percentage of zero in 1995, increasing to 12% in 2015. We have used these estimates in our modeling for 1995–2004, and for 2013–2015.

Romania

Data on LBs of DS in Romania are scarce and inconsistent. Zavate L. et al. (2012) report 16 LBs of DS, diagnosed in the Departments of Paediatrics and Paediatric Surgery in Cluj-Napoca, during 2003–2007. There were a total of 243,172 LBs in the two Romanian regions covered. This would suggest a prevalence of 0.65 per 10,000, which is so low that we have to assume huge under-ascertainment. Popa & Ghiorghiţa (2015) report 172 diagnoses of DS in LBs in two other Romanian regions during 2006–2013. On a total of 101,400 LBs, this implies a prevalence of 16.6 per 10,000, which is higher than the nonselective prevalence as estimated by our model. However, a more precise assessment of these data by year, reveals that out of the 172 diagnoses, 83 were from 2013, suggesting a prevalence of 65 per 10,000 in 2013, versus 10 per 10,000 for 2006–2012. The authors suggested that perhaps many cases born in earlier years were diagnosed in 2013, which seems to us a plausible explanation. However, as the data are apparently presented by year of diagnosis and not by year of birth, interpretation of the data is difficult.

Pop-Tudose M.E. et al. (2018) reported the use of prenatal screening for Down syndrome in 530 postpartum women, clients of Romania's south-east region maternities, during April-September 2016. Only 42% had done a prenatal screening or diagnostic test. The percentage of women of 35 years and older was similar in the ones who tested and the ones who did not, suggesting that there was not a higher uptake in the older age group. If screening tests had no false negatives, and assuming that uptake was similar in younger and older women, the reduction percentage would be 42%, too. However, the combined test, the most used prenatal strategy in Romania at the time,

misses 10% of the fetuses with DS (doi: 10.1002/14651858.CD012599). Taking this into account, reduction percentage as of 2016 would have been around 38%.

Madalina Turza of the European Centre for the Rights of Children with Disabilities communicated that, in Romania, starting in 2000, prenatal screening was only offered to older women or upon request (personal e-mail on August 3, 2017). This is corroborated by Gug et al. (2003) who reported the first year of offering amniocenteses in a hospital in Timisoara. They mention that pregnant women of 35 years and older should be offered the possibility of prenatal cytogenetic diagnosis, and that this in 2002 was not yet included in a Romanian national prenatal screening program.

According to Turza, until 2012, prenatal screening was offered only in the public health sector at a considerable cost. After 2012, upon request of the pregnant woman, she could be referred for the test; part or all of the costs, depending on the social income of the family, was covered by the state. We would expect that the policy before 2012 must have led to a relatively low reduction percentage, and that around 2000, the reduction percentage will have been zero. We have interpolated from zero in 2000 to 38% in 2015.

Russian Federation

For 2000–2011 data on births of children with Down syndrome in Russia were collected by The Federal Genetics Registry's "Monitoring of congenital malformations." Probably, this register contains live births and some (natural) stillbirths of children with DS. However, in these kinds of registries, stillbirths tend to be undercounted, and these only form a small proportion of cases. In U.S. registries, out of the total of registered live births and stillbirths with DS, only 4% were actually stillbirths (De Graaf et al., 2017, DOI: 10.1002/ajmg.a.38402). We assumed a similar percentage in the Russian registry.

Year of birth	Number of regions in Russia	Number of LBs in these regions	Number of live births with Down syndrome*	Live birth prevalence per 10,000 **
2000	24	468824	441	9.0
2001	31	607360	599	9.5
2002	31	631437	601	9.1
2003	30	622155	630	9.7
2004	24	500651	567	10.9
2005	31	605182	611	9.7
2006	33	673198	684	9.8
2007	37	765311	791	9.9
2008	37	840475	920	10.5
2009	40	924475	941	9.8
2010	43	947276	1132	11.5
2011	39	851788	1111	12.5

* Might contain a small percentage (around 4%) of stillbirths. ** excluding 4% possible stillbirths

In Russia, in the period 2006–2010, around 29% of potential births of children with DS were not born as a result of elective terminations; in the period 2001–2005, this was an estimated 25%. In the U.S., before 1980, the effect of elective terminations on the live birth prevalence of DS was still very small, with an estimated 6% reduction for the period 1975–1980, and less before (De Graaf et al. (2015), DOI 10.1002/ajmg.a.37001); we assumed the same would apply to Russia before 1980. We

interpolated the reduction between 1980–2000, assuming a gradual increase of this reduction in this period. In addition, we interpolated the reduction percentage for the period after 2011, assuming that the trend of a gradual increase of reduction continued into recent years to on average 33% for 2011–2015.

Slovakia
Data on LBs with DS are available for 1995–2012 for the country as a whole. According to Kádaši & Cisárik (2015), prenatal screening has been widely available since the 1970s in Slovakia. We have linearly extrapolated reduction percentage backwards in time from 25% in 1995-2000 to 0% in 1967. We have assumed that reduction percentage for 2013-2015 was similar to that in 2011-2012.

Ukraine
Data on LBs with DS are available for 2000-2015 for two provinces in Western Ukraine. For the period 2000–2015, these data cover on average 6% of the general births in Ukraine, with not much change between periods. As reduction percentage was estimated at zero for 2000-2004, we have assumed that this would also be the case before 2000.

S1D. Sources of actual LBs of children with DS

Western Europe

Austria

- EUROCAT (Table A5 - Down Syndrome (per 10,000 births)) EUROCAT Website Database: http://www.EUROCAT-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables (data uploaded 07/04/2017) (retrieved 4-July-2018) for Styria (1985–2012). For the period 1985–2012, the data cover on average 14% of the general births in Austria, varying between 13% for 2010–2012 to 15% for 1985–1989.

Belgium

- EUROCAT for Antwerp (1990–2014) and Hainaut (1980–2015)
- For Flanders as a whole (including Antwerp) 2009-2016: Het kind in Vlaanderen (reports 2011;2012;2013;2014;2015;2016) (The Child in Flanders) https://www.kindengezin.be/ (retrieved 12-Dec-2018). For the period 1980–2014, the data cover on average 27% of the general births in Belgium, varying between 7% for 1980–1984 to 27% for 2000–2004, 34% for 2005–2009 and 64% for 2010–2014.

France

- EUROCAT for Auvergne (2002; 2005–2015); Brittany (2011–2015; Paris (1981–2015); Strasbourg (1982–2007); Central East France (1980–2004); and Rhone Alps (2006–2012). For the period 1980–2014, the data cover on average 17% of the general births in France, varying between 13% for 2011–2015 to 21% for 1990–1994 and 1995–1999.
- For France as a total (including overseas territories), in “Le rapport médical et scientifique de l'assistance médicale à la procreation et de la génétique humaines en France”, l’Agence de la biomédecine has collected annual data on prenatal diagnoses of DS (including pregnancy outcomes after a prenatal diagnosis) since 2009, and on postnatal diagnoses of DS since 2010 (https://rams.agence-biomedecine.fr/archives).

Germany

- EUROCAT for Saxony-Anhalt (1987–2015) and for Mainz (1990–2014) (these two areas covering only 3% of all births in Germany).
- For Mecklenburg-Vorpommern 2002–2004, in: Renz I.C. (2006). Ergebnisse einer 3-jährigen Fehlbildungserfassung im Bundesland Mecklenburg-Vorpommern. Thesis. Ernst-Moritz-Arndt-Universität Greifswald.
- For West-Berlin 1980–1989 in: Sperling K. et al. (1994). Significant increase in trisomy 21 in Berlin nine months after the Chernobyl reactor accident: temporal correlation or causal relation? BMJ 1994;309, 158–62.
- For Bayern and Northern Bayern 1984–1989. In: Grosche B., Schoetzau A. & Burkart W. (1997). Down's Syndrome clusters in Germany in close temporal relationship to the Chernobyl accident. Radiation Research Vol. 147, No. 3 (Mar., 1997), 321–328.
- For Bayern. Schoetzau A., Irl, C., van Santen, F., Grosche B.& Müller U. (1997). Geburtsprävalenz ausgewählter Fehlbildungen bei Lebendgeborenen in Bayern von 1984–1991. Monatsschr Kinderheilkd 1997, 145:838–844.
- Deaths, cases per 100,000 inhabitants (age-standardized) (from 1998). Classification: years, region, age, sex, nationality, ICD-10, type of standardization. http://www.gbe-bund.de (retrieved 13-Dec-2018) (contains info on how many children with DS were registered as having died with DS as primary cause of death)
- Im Geburtsmonat behandelte Neugeborene: Deutschland, Jahre, Geschlecht, Wohnort des Patienten, Hauptdiagnose ICD-10 (from 2000). http://www.destatis.de (retrieved 5-March-2019)
- Krankenhauspatienten: Bundesländer, Jahre, Geschlecht, Altersgruppen, Hauptdiagnose ICD-10 (1-3-Steller Hierarchie) 2000–2017. http://www.destatis.de (retrieved 5-March-2019)
- Nippert, Irmgard und Neitzel, Heidemarie Ethische und soziale Aspekte der Pränataldiagnostik: Überblick und Ergebnisse aus interdisziplinären empirischen Untersuchungen Praxis der Kinderpsychologie und Kinderpsychiatrie 56 (2007) 9, S. 758-771 (info on number of invasive procedures in (former) West Germany in 1976, 1987, and 1995).
- Untersuchungen Praxis der Kinderpsychologie und Kinderpsychiatrie 56 (2007) 9, S. 758-771 (info on number of invasive procedures in (former) West Germany in 1976, 1987, and 1995).
- Der Einfluss pränataler Diagnostik und selektiven Fetozids auf die Inzidenz von Menschen mit angeborener Behinderung (https://www.ds-infocenter.de/downloads/lmds_49_mai2005.pdf p 10-15) (info on number of invasive procedures in (former) West Germany in 1970, 1982 and 1993).
- Lenhard W. (2004). Die psychosoziale Stellung von Eltern behinderter Kinder im Zeitalter der Pränataldiagnostik. Inaugural-Dissertation zur Erlangung der Doktorwürde der Philosophischen Fakultät III der Julius-Maximilians-Universität Würzburg. (info on number of amniocenteses and CVS in Bayern 1987-2003, based on BAQ, Bayerischen Arbeitsgemeinschaft für Qualitätssicherung in der stationären Versorgung)
- Lebendgeborene nach Geschlecht, Nationalität und Alter der Mütter - Jahressumme - regionale Ebenen. Statistik der Geburten. Statistische Ämter des Bundes und der Länder, Deutschland, 2019. (retrieved 4-March-2019)
- WPDT (1991–2005) [Annual reports of the Working Party Prenatal Diagnosis and Therapy (1991–2005)] Jaarverslagen Werkgroep Prenatale Diagnostiek en Therapie (WPDT) (1991–2005) Nederlandse Vereniging voor Obstetrie en Gynaecologie & Vereniging Klinische Genetica Nederland (in Dutch).

Luxembourg

- No data available

Netherlands

- For 1991–2015: De Graaf G., et al. (2017). Estimates of live birth prevalence of children with Down syndrome in the period 1991–2015 in the Netherlands. Journal of Intellectual Disability Research. doi: 10.1111/jir.12371
- For 1986–2007. De Graaf G., et al. (2011). Estimates of live birth prevalence of children with Down syndrome in the period 1991–2015 in the Netherlands. Journal of Intellectual Disability Research 55 (5), 462–473. doi: 10.1111/j.1365-2788.2011.01398.x
- For 1981–2015: EUROCAT
- Information about the percentage of women (of 38+ years of age) that participated in the screening for DS (with amniocentesis or CVS) on basis of the maternal age criterion (38+ for these years) in the period 1976-1984: Thomassen-Brepols L.J. (1985). Psychosocial aspects of prenatal diagnosis. Thesis Erasmus University, Rotterdam.

Switzerland

- For Switzerland 2003–2014. Numbers of livebirths of children with Down syndrome provided by the Federal Statistical Office. Published in: Hosali, R. (2017). Identifying the right business model for a digital community supporting differently abled individuals. Project Thesis of the University of St. Gallen, School of Management, Economics, Law and Social Sciences (HSG). University of St. Gallen, Switzerland.
- EUROCAT for Vaud (1989–2015)
- For 1980–1996: Binkert, F. & Schinzel, A. (2002). Impact of prenatal diagnosis on the prevalence of live births with Down syndrome in the eastern half of Switzerland 1980–1996. SWISS MED WKLY 2002; 132: 478–484.

Northern Europe

Denmark

- DS prenatal and postnatal diagnoses (in Danish) 1970–2017 http://www.auh.dk/siteassets/afdelinger/klinisk-genetisk-afdeling/dccr/pdf/downs-syndrom-1970-2017_figur1.pdf (retrieved 3-Dec-2018)
- DS live births 1990–2017 (in Danish) http://www.auh.dk/siteassets/afdelinger/klinisk-genetisk-afdeling/dccr/pdf/downs-syndrom-1970-2017_figur2.pdf (retrieved 3-Dec-2018)

Estonia

- DS live births 1990–2005 in Reimand, T. (2006). Down syndrome in Estonia. Dissertation at the Department of Paediatrics, University of Tartu, Estonia.
- DS live births 1990–2015 in Lokko (2016). Downi sündroomi levimus ja registreerimine Eestis. (Down syndrome prevalence and registration in Estonia) (in Estonian). Thesis at the Institute of Family Medicine and Public Health of the University of Tartu.
- DS live births 1990–2015 reported by the WHO Regional Office for Europe at https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births (retrieved 6-March-2019), based on maternity hospital data (1990–1995), the National Institute for Health Development (1996–1999), Genetics Centre of the Tartu University Hospital (1999 onwards).

Finland

- National data on births of DS, 1974–1999: http://urn.fi/URN:NBN:fi-fe201205085015 (1993-2009 epidemiological report of The National Institute for Health and Welfare (THL)). (We have not used the data 1974–1986 as we suspect severe underascertainment for this period)
- For 2000-2014: http://urn.fi/URN:NBN:fi-fe2018062626441 (2014 epidemiological report of The National Institute for Health and Welfare (THL)).
- For 1993–2011, EUROCAT.

Iceland

- Full information on LBs of children with DS for 1985–2017 is available from the State Diagnostic and Counselling Centre (in Islandic) at https://www.greining.is/is/moya/page/downs-heilkenni-a-islandi and/or http://www.downs.is/files/5ab0f1558efde.pptx (retrieved 13-Nov-2018)

Ireland

- EUROCAT for Cork and Kerry (1996–2015); Dublin (1980–2012); Galway (1981–1999); South-East Ireland (1997–2014); For the period 1980–2015, the data cover on average 49% of the general births in Ireland, varying between around 40% for 1980–1985, 1986–1990, 1991–1995, 2011–2015 to around 60–65% for 1996–2000, 2001–2005, and 2006–2010.

Latvia

- Data on LBs of children with DS are available for 1990–2015, reported by the WHO Regional Office for Europe (at https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births/), based on the Register of Congenital Anomalies in Latvia.

Lithuania

- Data on LBs of children with DS are available for 1992–2015, reported by the WHO Regional Office for Europe (at https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births/), based on the Medical Genetics Centre (up to 2001) and the Medical Birth Register (from 2002); Coverage: Newborns with Down syndrome.

Norway

- 1967–2016. Medisinsk fødselsregister – statistikkbank. M1: Medfødte misdannelser. Registrerte med alle og utvalgte medfødte misdannelser. http://statistikkbank.fhi.no (retrieved 13 March 2019)
- 1999–2012 EUROCAT (whole country)
- 1967–1976: Bjerkedal T.& Kristensen P. (2007) Live born in Norway 1967-76 with the diagnosis of Down syndrome [Levendefødte i Norge 1967-76 med diagnosen Down syndrom En registerstudie], Norsk Epidemiologi 17(2):157-164.

Sweden

- 2007–2012 EUROCAT (whole country)
- 1999–2010 Clearinghouse Annual Report 2012

- 1974–2003 Englund 2013 DOI: 10.1002/ajmg.a.35706
- 1973–2016 Rapport över Fosterskador och kromosomavvikelser 2016 (Birth defects 2016). Annual report from the Swedish Birth Defects Registry.

United Kingdom

Great Britain

- EUROCAT for East Midlands & South Yorkshire (1998–2012); Glasgow (1980–2000); Merseyside & Cheshire (1995–1999); Northern England (2000–2015); N W Thames (1991–2004); South West England (2005–2015); Thames Valley (1991–2015); Wales (1998–2015); and Wessex (1994–2015).

England/Wales

- Data on LBs with DS 1989–2013. Morris, J.K. & Springett A. (2014). The National Down Syndrome Cytogenetic Register for England and Wales: 2013 Annual Report. London. National Down Syndrome Cytogenetic Register: London. http://www.binocar.org/content/annrep2013_FINAL.pdf (retrieved 3-Dec-2018)
- Estimates of LBs on basis of data on abortions of fetuses with DS 1974-1987: Cuckle H., Nanchahal K. & Wald N. (1991) Birth prevalence of Down's syndrome in England and Wales. Prenatal Diagnosis 11, 29–34.
- Data on abortions of fetuses with DS 1987–1997: Botting, B. & ONS. Improving the completeness of Down syndrome notification Health Statistics Quarterly 06. Summer 2000. http://www.ons.gov.uk/ons/rel/hsq/health-statistics-quarterly/no--6--summer-2000/improving-the-completeness-of-down-syndrome-notification.pdf

Scotland

- Data on LBs with DS for 1991–2011: Scottish Perinatal and Infant Mortality and Morbidity Reports (2001 to 2012), Healthcare Improvement Scotland. https://www.isdscotland.org/Health-Topics/Maternity-and-Births/Publications/ (retrieved 3-Dec-2018)
- For 1978–1992: Huether C. A., Haroldson K., Ellis P. M. & Ramsay C. N. (1996) Impact of prenatal diagnosis on revised livebirth prevalence estimates of Down Syndrome in the Lothian Region of Scotland, 1978-1992. Genetic Epidemiology 13, 367–375.

Northern Ireland

- Data on LBs with DS for 2007–2016. Director of Public Health Core Tables 2016. Supporting the Director of Public Health Annual Report 2017. http://www.publichealth.hscni.net/sites/default/files/Core%20Tables%202016%20-%20final%20-%208%20Dec%202017_0.pdf (retrieved 3-Dec- 2018)
- For 2008 in Prevalence and primary prevention of congenital anomalies in Northern Ireland. Ulster University. http://uir.ulster.ac.uk/37141/1/NICAREport.pdf (retrieved 3-Dec-2018)

Southern Europe

Albania

- Data on LBs with DS for 2011 and 2012: Çanaku, D., et al.'s Epidemiology of congenital malformations in Albania during 2011–2012. Institute of Public Health. http://www.ishp.gov.al/epidemiology-of-congenital-malformations-in-albania-during-2011-2012/ (accessed August 8, 2019). The reported births of children with DS are LBs, in personal e-mail by D. Çanaku (August 12, 2019).
- Data on LBs with DS 2013–2018: personal e-mail by D. Çanaku (September 10, 2019). The results are based on data from cytogenetic diagnoses in Albania and can be considered to be complete (personal e-mail D. Çanaku, September 11, 2019)

Bosnia and Herzegovina

- Data on LB prevalence of DS in Bosnia and Herzegovina for 2005–2018: Kurtovic-Kozaric A., et al. (2016). Ten-year trends in prevalence of Down syndrome in a developing country: impact of the maternal age and prenatal screening. *EJOG* 206: 79-83. https://doi.org/10.1016/j.ejogrb.2016.08.038

Croatia

- EUROCAT for Zagreb (1983–2015), combined with data for the Region of Primorskogoranska for 1996–2005. From Bojana Brajenović-Milić B. & T Petrović O. (2007). The Impact of Screening and Amniocentesis on the Prevalence of Live Birth Down Syndrome in the Region of Primorskogoranska. *Maternal and Child Health Journal* · September 2007. DOI: 10.1007/s10995-007-0272-6. For the period 1983–2015, the data cover on average 14% of the general births in Croatia, with 6% for 1983–1985, 12% for 1986–1990, 13% for 1991–1995, 17% for 1996–2000, 19% for 2001–2005, 19% for 2006–2010, and 15% for 2011–2015
- Data on LBs with DS in Croatia for 2009–2012: Glivetic, T., et al. (2015). Prevalence, prenatal screening and neonatal features in children with Down syndrome: a registry- based national study. *Italian Journal of Pediatrics* 41: 81. doi: 10.1186/s13052-015-0192-9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4625928/
- Number of persons with DS by year of birth, alive in Croatia, as of 2015 and 2018: These data are collected by the Croatian Institute of Public Health. We received these by personal e-mail (August 21, 2019) from Dinka Vukovic of Croatia Down Syndrome Association.

Greece

- Number of invasive prenatal procedures in Greece, in 1976, 1980, and 1984: Velogiannis – Moutsopoulos L. & Bartsocas C.S. (1989). Ethics and medical genetics in Greece. In: Ethics and Human Genetics: A Cross-Cultural Perspective. D. C. Wertz & J. C. Fletcher (eds). Springer-Verlag. Berlin, Heidelberg, New York.
- Number of invasive prenatal procedures in Greece in 1995: Metaxotou C, Mavrou A, & Antsaklis A. (1997). Prenatal Diagnosis Services in Greece. *Eur J Hum Genet* 5:39–41. DOI:10.1159/000484814
- Attitudes of physicians, midwives, press, and pregnant women towards prenatal screening in Greece (compared to other European countries) in the period 1996–1999: Ettorre, E. (2018). A European project on the development of prenatal screening. In: Before Birth: Understanding Prenatal Screening. E. Ettorre (ed). Routledge. New York.

- Attitudes, perceptions and ideas relating to prenatal diagnostics of Greek pregnant women (compared to other European countries) in the period 2005–2008: Samakouri M., et al. (2018). Comment C, concerning empirical data from a Greek perspective. In: The Janus Face of Prenatal Diagnostics: A European Study Bridging Ethics, Psychoanalysis and Ethics. E. Engels, M. Leuzinger-Bohleber& J. Tsiantis Routledge. New York
- Attitudes towards and knowledge of prenatal screening in Greek pregnant women: Gourounti K. & Sandall J. (2008). Do pregnant women in Greece make informed choices about antenatal screening for Down's syndrome? A questionnaire survey. *Midwifery*. 2008 Jun;24(2):153-62. Epub February 20, 2007.

Italy

- EUROCAT for Campania (1996–2004); Emilia Romagna (1981–2016); North East Italy (1981–2003); Sicily (1991–2004); and Tuscany (1980–2016). For the period 1980–2014, the data cover on average 18% of the general births in Italy, with 9% for 1980–1984, 13% for 1985–1989, 20% for 1990–1994, 30% for 1995–1999, 32% for 2000–2004, 13% for 2005–2009, and 13% for 2010–2014.

Malta

- EUROCAT for Malta (1986–2016)

Montenegro

- Policy related to prenatal diagnostics in Montenegro: OECD (2006). Education Policies for Students at Risk and those with Disabilities in South Eastern Europe. Organisation for Economic Co-operation and Development (OECD).
- Policy related to prenatal diagnostics in Montenegro: Government of Montenegro (2009). Consumer and health protection. Questionnaire. Information requested by the European Commission to the Government of Montenegro for the preparation of the Opinion on the application of Montenegro for membership of the European Union. Government of Montenegro, Ministery of Economy. Podgorica.

North Macedonia

- Information on the history of amniocentesis and CVS in North Macedonia: Sukarova–Angelovska E. & Petlichkovski A. (2018). Genetics in Macedonia—Following the international trends. *Mol Genet Genomic Med.* 6(1): 9–14.
- LBs with DS by maternal age group in Skopje: Zisovska E. & Lazovska B. (2006). Down Syndrome - The Incidence And Risks. *Balkan Journal of Medical Genetics* vol 9 (3&4). p. 76

Portugal

- EUROCAT for Southern Portugal (1990–2016); For the period 1990–2015, the data cover on average 15% of the general births in Portugal, with 8% for 1990–1994, 15% for 1995–1999, 17% for 2000–2004, 19% for 2005–2009, and 20% for 2010–2014.
- Centro De Estudos E Registo De Anomalias Congénitas Relatório de 2000–2001 (http://repositorio.insa.pt/handle/10400.18/1644); accessed August 10, 2019) reports the number of LBs of children with DS in the whole of Portugal in 2000 and 2001.

Serbia (including Kosovo)

Serbia

- Dimitrijevic A. et al. (2013). The incidence of Down syndrome in newborns at the Department of Obstetrics and Gynecology of the Clinical center Kragujevac during the period 2007–2012. *Medicinski Casopis* 47(1):12-16. DOI: 10.5937/mckg47-1425
- Number of prenatal diagnoses of DS in Southern and Eastern Serbia during 2004–2017: Milićević , R. et al. (2019). Fetal chromosomal anomalies in Southeast Serbia—single center cohort retrospective study. *Genetika* 51 (1): 157-166. https://doi.org/10.2298/GENSR1901157M
- DS birth prevalence 2006–2015 is reported by the WHO Regional Office for Europe at https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births (accessed September 17, 2019) based on data of the Institute of Public Health of Serbia. Birth registration report. Data includes congenital malformations diagnosed (ICD10: Q90) after birth and before discharge of newborn from the maternity ward.

Kosovo

- LBs of children with DS in Kosovo 2000–2010: Kolgeci, S., et al. (2013). Cytogenetic Study in Children with Down Syndrome Among Kosova Albanian Population Between 2000 and 2010. *Mater Sociomed* 25(2): 131–135.

Slovenia

- Information on number of prenatal and postnatal diagnoses of DS in Slovenia for 1982–2012: Rudolf, G., et al. (2017). Impact of prenatal screening on the prevalence of Down syndrome in Slovenia. *PLoS One*. 2017 Jun 30;12(6):e0180348. doi: 10.1371/journal.pone.0180348. eCollection 2017.
- DS birth prevalence 1988–2015 is reported by the WHO Regional Office for Europe at https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births (accessed September 17, 2019) based on data from the National Institute of Public Health, Slovenia (NIJZ). Whether SBs or TOPs are included is not specified.

Spain

- EUROCAT for Asturias (1990–2004); Barcelona (1992–2007); Basque Country (1990–2015); Spain Hospital Network (1980–2012); and Valencia Region (2007–2016). For the period 1980–2014, the data cover on average 26% of the general births in Spain, with 12% for 1980–1984, 13% for 1985–1989, 30% for 1990–1994, 36% for 1995–1999, 34% for 2000–2004, 34% for 2005–2009, and 26% for 2010–2014.

Eastern Europe

Belarus

- Total birth prevalence and LB prevalence for DS by year for 1981–2001: Zatsepin, et al. (2004). Cluster of Down's syndrome cases registered in January 1987 in Republic of Belarus

as a possible effect of the Chernobyl accident. *International Journal of Radiation Medicine* 6(1-4): 57-71.

- DS as morbidity in children aged 0–1 years (1997–2015) reported by the WHO Regional Office for Europe at https://gateway.euro.who.int/en/indicators/hfa_603-7120-births-with-downs-syndrome-per-100-000-live-births (accessed March 6, 2019).

Bulgaria

- 1996–1999 EUROCAT (Sofia)
- Number of LBs with DS in 2008–2012 in Bulgaria: Yankova M. & Savov A. (2014) [Types of screening for congenital diseases - results in Bulgaria, conclusions and future objectives].[Article in Bulgarian]. *Akush Ginekol* (Sofiia) 53(3):13-20.
- Attitudes towards and use of prenatal testing by Bulgarian women: Levkova, et al. (2018). Women's Awareness Towards Prenatal Down Syndrome Tests in Bulgaria. *J Down Syndr Chr Abnorm* 4:2. DOI: 10.4172/2472-1115.1000129

Czech Republic

- 2000–2010 EUROCAT (whole country)
- 1974–2012 Clearinghouse Annual Report 2014
- Sípek, A., et al. (2009). Down syndrome in the Czech Republic during 1961–1997: prevalence, prenatal diagnosis and maternal-age-specific rates. *J Obstet Gynaecol*. 2001 May;21(3):266-9. DOI: 10.1080/01443610120046387

Hungary

- 1998–2012 EUROCAT (whole country)
- 1974–2012 Clearinghouse Annual Report 2014
- Information on the history of prenatal diagnostics in Hungary: Czeizel A. (1988). Medical genetics in Hungary. *Journal of Medical Genetics* 25, 2–8.

Poland

- 1999–2015 EUROCAT (whole country)
- Number of LBs with DS in Southern Poland in the mid-eighties: Pietryzyk J.J. & Majerska B. (1987). Epidemiology of Down's syndrome in Southern Poland. *Pediatric Research* 22:238.

Republic of Moldova

- Number of LBs of children with DS and number of prenatal diagnoses of DS in Moldovia in 2005–2012: Barbova, N., et al. (2014). Effectiveness of prenatal Down syndrome cytogenetic diagnosis. Bulletin of the Academy of Sciences of Moldova. Medical Sciences. Number 1 (42) / 2014 / ISSN 1857-0011: p. 116-222

Romania

- LBs of children with DS in 2006–2013 in 2 Romanian regions (Bacau and Vaslui): Popa, C. & Ghiorghiţa, G. (2015). Frequency of congenital malformations and chromosomal disorders in Bacau and Vaslui counties (Romania). *J. Genet*. 94(4):661-8. DOI: 10.1007/s12041-015-0579-9
- LBs of children with DS in 2003–2007 in 2 Romanian regions (NW and SW): Zavate, L., et al. (2012). Study of prevalence and birth defects types in the children from two development regions of Romania: NW and SW. *Acta Medica Transilvanica* 2(1):162-164.

- Attitude towards and use of prenatal screening for Down syndrome in 530 postpartum women, clients of Romania's southeast region maternities, during April–September 2016: Pop-Tudose, M.E., et al. (2018). Attitude, knowledge and informed choice towards prenatal screening for Down Syndrome: a cross-sectional study. *BMC Pregnancy Childbirth* 18: 439. Doi: 10.1186/s12884-018-2077-6
- History of amniocentesis in Romania: Gug et al. (2003). Prenatal Cytogenetic Diagnosis in Timisoara: 1 Year Experience. *Timisoara Medical Journal* 53 (2).

Russian Federation

- 2000–2011 data on births of children with Down syndrome collected by The Federal Genetics Registry's "Monitoring of congenital malformations."

Slovakia

- 1995–2012 Clearinghouse Annual Report 2014
- Information about the history of prenatal screening in Slovakia: Kádaši, L. & Cisárik, F. (2015). Genetics and genomic medicine in Slovakia. *Mol Genet Genomic Med* 3(1): 8–13. doi: 10.1002/mgg3.122

Ukraine

- 2005–2016 EUROCAT for two provinces in Western Ukraine
- 2000–2012 Clearinghouse Annual Report 2014 for two provinces in Western Ukraine

S2. Number of live births in general population before 1950

S2A. Constructing live birth estimates

If data on numbers of live births in general population before 1950 were known, we used these data (see S2B).

However, for some countries, numbers of live births in general population before 1950 were unknown. As an alternative for these countries, we constructed estimates of these numbers on basis of 1955- and 1950-population age structure (in combination with 1-year mortality constructs for the general population and a correction for mortality above 1 year of age on basis of precise information from the UK and the Netherlands on actual birth numbers for 1900-1950). To validate this approach, we constructed these estimates for all countries, so we could compare these with reported numbers, if known. In any case, if there were reported numbers, we used these in our estimations. However, for validation purposes, we constructed estimates on basis of 1955-and 1950-population age structure for all countries.

In constructing these estimates, we used the following procedure. We assumed that the number still alive in 1955, aged 0-4 years, gives an indication for the ones born in 1950–1954. For each country separately, we applied 1-year survival rates (as reported by country for 1950–1955 in the World Population Prospects of the United Nations Population Division) to the numbers alive, aged 0-4 years in 1955. If 1-year survival for the period 1950–1954 for instance equaled 0.97, the number of births predicted for 1950–1954 will be the number alive, aged 0–4 years in 1955, divided by 0.97. The next step is checking whether these numbers of births predicted for 1950–1954 equals the numbers of births as reported by the United Nations Population Division for the same period. If this was a bit off (as should be expected as there is also mortality between 1 and 5 year of age), we made a correction factor to make a perfect fit. For instance, it might be a perfect fit if multiplied by 1.002.

Subsequently, we assumed that the number still alive in 1955, aged 5–9 years, gives an indication for the number of births between 1945–1949. We divided these number still alive by the 1-year survival rates as constructed for the period 1945–1949 (see Supplementary Materials S4). Subsequently, we multiplied these with the correction factor explained above. We continued this procedure for earlier years, using the number of 10–14 years in 1955 to predict the number of births for 1940–1944, etc. However, in these first estimations, mortality above 5 years of age is ignored, producing increasing underestimations for earlier years. We had to construct a second correction factor.

This second factor is based on data from the UK and the Netherlands. For both countries, national statistical offices have reliable data available on the total number of births going back to 1900. Comparing the predicted numbers of births (as estimated by the method described above) for these countries with the reported number of births reveals that the predictions indeed are underestimations, discrepancy growing when going further back in time. We constructed separately for the UK and the Netherlands a correction factor for each five-year period, which if applied changes the predicted numbers into the reported numbers. We plotted these correction factors for the UK and the Netherlands, against the five-year periods on the x-axis in one graph and made the best fit by using linear regression. The derived correction factors increase from 1 for the period 1945–1950, 0.9844 for 1940–1944 to 0.814 for 1900–1904. The earlier predicted numbers of births were divided by these correction factors to produce the definitive predictions.

Validating the predictions

We compared the predicted numbers of births for the 5-year periods between 1930 and 1950 with reported numbers, if available (see section S2B). The numbers before 1930 are less important. Persons born before 1930 would be over 85 years of age in 2015, and only very few people with DS survive over 85 years of age.

For 1945–1949, we had data on births in general population for 37 European countries. For 25 countries the predicted numbers were less than 5% different from the reported numbers. For 8 countries, the difference ranged between 5-10%; for 3 countries between 10-20%; and for 1 country, the Republic of Moldova, the model estimates were 32% lower than the reported numbers. There was an extreme famine in 1946 and 1947 in Moldova leading to many deaths and a decrease in population size (https://en.wikipedia.org/wiki/Soviet_famine_of_1946–47). As young children are more likely to be victims during a famine, the number of children alive, aged 5–9 years in 1955, is probably much lower than you would expect in more normal circumstances, and as these numbers were used to estimate the numbers of births between 1945–1949, this might explain why these birth estimates are underestimates. For 1945–1949, we had to use modeled estimates for 2 countries (as we could not find reported numbers): Belarus; Serbia.

For 1940–1944, we had data on births in general population for 27 European countries. For 14 countries, the predicted numbers were less than 5% different from the reported numbers. For 7 countries, the difference ranged between 5-10%; for 4 countries between 10-20%. For 2 countries, the difference was 20% or more: Czech Republic (model underestimates by -25%) and Estonia (model overestimates by +32%). For 1940–1944, we had to use modeled estimates for 12 countries, alphabetically: Albania, Belarus, Bosnia and Herzegovina, Croatia, Lithuania, Montenegro, North Macedonia, Poland, Republic of Moldova, Romania, Serbia, and Ukraine

For 1935–1939, we had data on births in general population for 31 European countries. For 15 countries, the predicted numbers were less than 5% different from the reported numbers. For 5 countries, the difference ranged between 5-10%, for 6 countries between 10-20%. For 5 countries, the difference was 20% or more: Albania (model overestimates by +20%); Czech Republic (model underestimates by -25%); Estonia (+37%); Latvia (+21%); Poland (-35%); Romania (-31%). For some of these countries, this discrepancy might be the result of migration. For instance, in 1940–1944 there was a strong migration out of Latvia, followed by a strong immigration into Latvia in 1945–1949 (as can be deducted from the data on population size, births and deaths on (https://en.wikipedia.org/wiki/Demographics_of_Latvia). These migrations affect population numbers by age in later years, and this might explain why the predictions of earlier births on the basis of these later population numbers are off target. In addition, WWII may have taken a very high toll of lives in some countries, which certainly is the case for Poland (https://ww2db.com/country/poland). The resulting lower population numbers probably explain why the model predicts too low numbers of births for the period before 1945. For 1935–1939, we had to use modeled estimates for 8 countries, alphabetically: Belarus, Bosnia and Herzegovina, Croatia, Montenegro, North Macedonia, Republic of Moldova, Serbia, and Ukraine.

For 1930–1934, we had data on births in general population for 30 European countries. For 14 countries, the predicted numbers were less than 5% different from the reported numbers. For 5 countries, the difference ranged between 5-10%, for 6 countries between 10-20%. For 5 countries, the difference was 20% or more: Czech Republic (-22%); Estonia (+37%); Latvia (+22%); Poland (-32%); Romania (-29%). Again, probably these discrepancies are explained by migrations and/or extreme loss of lives during WWII and/or in the period 1945–1950. For 1930–1934, we had to use

modeled estimates for 9 countries, alphabetically: Belarus, Bosnia and Herzegovina, Croatia, Montenegro, North Macedonia, Republic of Moldova, Serbia, and Ukraine.

For the period before 1950, if available, we used reported numbers (see S2B). If not, we used our predicted numbers, as explained above.

S2B. Sources for number of LBs in general population before 1950

Western Europe

Austria
Years: 1900-1950
Source: DYB (Demographic Yearbook Collection of the United Nations; https://unstats.un.org/unsd/demographic-social/products/dyb/ statistics for 1936-1950; and https://en.wikipedia.org/wiki/Demographics_of_Austria#Vital_statistics_since_1900 which refers to: http://statistik.at/web_de/statistiken/index.html (Statistik Austria)

Belgium
Years: 1900-1950
Source: DYB for 1939-1950; and
https://en.wikipedia.org/wiki/Demographics_of_Belgium#Vital_statistics_from_1900
which refers to: https://statbel.fgov.be/nl (Statbel, the Belgian statistical office)

France
Years: 1900-1950
Source: DYB for 1936-1950; and
https://en.wikipedia.org/wiki/Demographics_of_France#Vital_statistics_from_1900
which refers to: https://www.ined.fr/fr/tout-savoir-population/chiffres/bases-donnees/donnees-pays-developpes/ (L'Institut national d'études démographiques (Ined))

Germany
Years: 1900-1950
Source: DYB for 1936-1938 and 1947-1948; and
https://en.wikipedia.org/wiki/Demographics_of_Germany
which refers to: https://www.destatis.de (Statistische Bundesamt)

Luxembourg
Years: 1900-1950
Source: DYB for 1936-1950; and
https://en.wikipedia.org/wiki/Demographics_of_Luxembourg#Vital_statistics_since_1900
which refers to: http://statistiques.public.lu/fr/ (Statec, Statistics Portal of Luxembourg)

Netherlands
Years: 1900-1950
Source https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37556/table?ts=1536835324571 (Table of the Dutch Statistical Office on the growth of the population and live births as of 1899)

Switzerland
Years: 1900-1950
Source: DYB for 1936-1946 and 1948-1950; and

https://en.wikipedia.org/wiki/Demographics_of_Switzerland
which refers to: https://www.bfs.admin.ch/bfs/en/home.html (Federal Statistical Office of Switzerland), and https://unstats.un.org/unsd/demographic/products/dyb/dybsets/1948%20DYB.pdf (Demographic Yearbook 1948 (PDF). Statistical Office of the United Nations.)

Northern Europe

Denmark
Years: 1900-1950
Source: DYB for 1936-1950; and https://en.wikipedia.org/wiki/Demographics_of_Denmark
which refers to: http://www.statistikbanken.dk/statbank5a/default.asp?w=1366 (Retrieved 29 August 2017)

Estonia
Years: 1915-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Estonia
which refers to: http://pub.stat.ee/px-web.2001/I_Databas/Population/01Population_indicators_and_composition/02Main_demographic_indicators/02Main_demographic_indicators.asp (Main demographic indicators. Statistics Estonia)

Finland
Years: 1900-1950
Source: DYB for 1936-1950; and https://en.wikipedia.org/wiki/Demographics_of_Finland
which refers to: http://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin__vrm__kuol/?tablelist=true (Statistics Finland List of Tables in English), and http://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin__vrm__synt/statfin_synt_pxt_003.px (Live births by year)

Iceland
Years: 1900-1950
Source: DYB for 1936-1950; and https://en.wikipedia.org/wiki/Demographics_of_Iceland
which refers to: https://www.statice.is/

Ireland
Years: 1900-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_the_Republic_of_Ireland
which refers to: Central Statistics Office

Latvia
Years: 1920-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Latvia
which refers to: http://data.csb.gov.lv (Statistical Office of Latvia)

Lithuania
Years: 1915-1940;1945-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Lithuania
which refers to: https://www.stat.gov.lt/lt/pages/view/?id=2714 (Statistical Yearbooks of Lithuania)

Norway
Years: 1900-1950

Source: DYB for 1936-1950; and https://en.wikipedia.org/wiki/Demographics_of_Norway
which refers to: https://www.ssb.no/en/ (Statistics Norway)

Sweden
Years: 1900-1950
Source: DYB for 1936-1950; and https://en.wikipedia.org/wiki/Demographics_of_Sweden
which refers to: http://www.scb.se/en_/ (Statistics Sweden)

United Kingdom
Years: 1900-1950
Source: https://www.statista.com/statistics/281956/live-births-in-the-united-kingdom-uk-1900-1930/; and https://www.statista.com/statistics/281965/live-births-in-the-united-kingdom-uk-1931-1960/

Southern Europe

Albania
Years: 1935-1940; 1949-1950
Source: DYB for 1948 and 1950; and https://en.wikipedia.org/wiki/Demographics_of_Albania
which refers to: B.R. Mitchell. European historical statistics, 1750-1975

Bosnia and Herzegovina
Years: 1947-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Bosnia_and_Herzegovina
which refers to: https://www.ined.fr/fr/tout-savoir-population/chiffres/bases-donnees/donnees-pays-developpes/ (L'Institut national d'études démographiques (Ined))

Croatia
Years: 1900-1915; 1947-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Croatia
which refers to: Brian R. Mitchell (1980). European historical statistics, 1750-1975

Greece
Years: 1921-1950
Source: DYB for 1936-1938; and https://en.wikipedia.org/wiki/Demographics_of_Greece
which refers to: R. Mitchell. European historical statistics, 1750-1975;
https://unstats.un.org/unsd/demographic/products/dyb/dybsets/1948%20DYB.pdf (Demographic Yearbook 1948 (PDF). Statistical Office of the United Nations.)

Italy
Years: 1900-1950
Source: DYB for 1936-1943, 1945 and 1948-1950; and
https://en.wikipedia.org/wiki/Demographics_of_Italy
which refers to: R. Mitchell. European historical statistics, 1750-1975, and
https://unstats.un.org/unsd/demographic/products/dyb/dybsets/1948%20DYB.pdf (Demographic Yearbook 1948 (PDF). Statistical Office of the United Nations.)

Malta
Years: 1932-1950
Source: DYB for 1932-1950; and https://en.wikipedia.org/wiki/Demographics_of_Malta

which refers to: https://unstats.un.org/unsd/demographic/products/dyb/dybsets/1948%20DYB.pdf (Demographic Yearbook 1948 (PDF). Statistical Office of the United Nations.)

Montenegro
Years: 1947-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Montenegro
which refers to: http://www.monstat.org/cg/page.php?id=47&pageid=47 (statistical office of Montenegro)

North Macedonia
Years: 1947-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_the_Republic_of_Macedonia
which refers to: http://www.stat.gov.mk/ (State Statistical Office of the Republic of Macedonia)

Portugal
Years: 1900-1950
Source: DYB for 1936-1950; and https://en.wikipedia.org/wiki/Demographics_of_Portugal
which refers to: R. Mitchell. European historical statistics, 1750-1975, and https://unstats.un.org/unsd/demographic/products/dyb/dybsets/1948%20DYB.pdf (Demographic Yearbook 1948 (PDF). Statistical Office of the United Nations.); and

Serbia (including Kosovo)
Years: 1900-1912
Source: https://en.wikipedia.org/wiki/Demographic_history_of_Serbia#1900%E2%80%931912
which refers to: B.R. Mitchell. European historical statistics. 1750-1975.

Slovenia
Years: 1900-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Slovenia
which refers to: https://www.stat.si/ (Statistical Office of the Republic of Slovenia)

Spain
Years: 1900-1950
Source: DYB for 1936-1950; and https://en.wikipedia.org/wiki/Demographics_of_Spain
which refers to: http://www.ine.es/inebaseweb/25687.do (Statistical Yearbooks of Spain)

Eastern Europe

Belarus
Years: 1900-1915
Source: https://en.wikipedia.org/wiki/Demographics_of_Belarus
which refers to: http://istmat.info/node/21366 (Statistical Yearbooks of Russia)

Bulgaria
Years: 1900-1950
Source: DYB for 1938-1944 and 1949-1950; and
https://en.wikipedia.org/wiki/Demographics_of_Bulgaria
which refers to: B.R. Mitchell. European historical statistics, 1750–1975, and Demographic Yearbook 1948 (PDF). Statistical Office of the United Nations. Retrieved 20 February 2015, and "National

Statistical Institute of Bulgaria". Archived from the original on 31 July 2010. Retrieved 10 October 2014

Czech Republic
Years: 1900-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_the_Czech_Republic
which refers to: Czech Demographic Handbook 2007". Czech Statistical Office

Hungary
Years: 1900-1950
Source: DYB for 1937-1938, 1945-1946 and 1948-1950; and
https://en.wikipedia.org/wiki/Demographics_of_Hungary
which refers to: B.R. Mitchell. European historical statistics, 1750–1975, and
http://unstats.un.org/unsd/demographic/products/dyb/dybsets/1948%20DYB.pdf United nations. Demographic Yearbook 1948, and "Vital statistics, Hungarian Central Statistical Office". ksh.hu. Retrieved 2015-05-18; "Developed Countries Demography". Institut National d'Études Demographiques - INED. Retrieved 5 September 2017

Poland
Years: 1920-1940; 1946-1950
Source: DYB for 1932-1939; and https://en.wikipedia.org/wiki/Demographics_of_Poland
which refers to: B.R. Mitchell. European historical statistics, 1750-1975, and "United Nations: Demographic Yearbook 1948" (PDF). Unstats.un.org. Retrieved 30 August 2017, "Archived copy". Archived from the original on 2008-09-17. Retrieved 2008-08-29.

Republic of Moldova
Years: 1900-1915; 1945-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Moldova
which refers to: http://istmat.info/node/21366 (Statistical Yearbooks of the Russian Empire);
http://unstats.un.org/unsd/demographic/products/dyb/dyb2.htm#2001 United nations. Demographic Yearbooks; Statistica Moldovei

Romania
Years: 1900-1915; 1920-1942; 1946-1950
Source: DYB for 1936-1942; and https://en.wikipedia.org/wiki/Demographics_of_Romania
which refers to: "Eurostat - Tables, Graphs and Maps Interface (TGM) table". Epp.eurostat.ec.europa.eu. Retrieved 3 October 2017, and "Bun venit la Institutul National de Statistica - Institutul National de Statistica". Insse.ro. Retrieved 3 October 2017

Russian Federation
Years: 1900-1915; 1925-1950
Source: “Long-Term Population Statistics for Russia, 1867-2002 Russian Research Center, The Institute of Economic Research, Hitotsubashi university, Kunitachi, Tokyo, Japan.”

Slovakia
Years: 1920-1950
Source: https://en.wikipedia.org/wiki/Demographics_of_Slovakia
which refers to: no references

Ukraine
Years: 1900-1915; 1946-1950

Source: https://en.wikipedia.org/wiki/Demographics_of_Ukraine
which refers to: http://istmat.info/node/21366 (Statistical Yearbooks of Russia) for 1900-1915

S3. Live birth prevalence of DS before 1950

S3A. Constructing estimates for live birth prevalence of DS

For some countries, data on maternal age distribution before 1950 are available (for the period 1936–1950 in the DYB; and for the UK and the Netherlands in national statistics, see S3B). For those countries, the number of LBs of children with DS can be estimated by applying the maternal age-specific chances for a LB of a child with DS, to the numbers of LBs in general population by maternal age.

We used the most recent model of maternal-age specific chances, based on the largest sample, developed by Morris et al. (2002). First, we constructed 5-year maternal age-specific chances by year of birth by applying the single-year chances from the model of Morris to the U.S. birth data with single-year maternal age bands, available for 1931–1937 and 1946–1950 (and also from 1950 onwards) in the Vital Statistics of the United States (https://www.cdc.gov/nchs/products/vsus.htm). We interpolated these 5-year maternal age-specific chances for 1938–1945. The 5-year maternal age-specific chances evolve slightly over the years in the U.S. sample (as the maternal age distribution within these 5-year bands changes over time), and we have assumed that this would apply to the European samples, too. The use of these constructed 5-year maternal age-specific chances by year of birth is fine-tuning with only slight effects on the estimates of the LBs of children with DS. Alternatively, if one applies 2015-based 5-year maternal age-specific chances to the U.S. Vital Statistics data on maternal age by 5-year group, this yields for the 1930s an only 2% lower estimate of the number of LBs of children with DS, in comparison to using the constructed 5-year maternal age-specific chances by year of birth. For the 1940s, the difference between the approaches is less than 1%. For countries with data on maternal age distribution, we applied these constructed 5-year maternal age-specific chances by year of birth to the number of births by 5-year maternal age group (by year of birth).

If data on maternal age distribution were lacking, as an alternative, we constructed estimates of number of live births by maternal age on basis of the female population by 5-year age group in 1950, and the age-specific fertility in 1960, 1955, and 1950. If you want to know how many children with DS were born in 1945, you need to know how many women there are in 5-year age groups in 1945—and what their fertility was.

The first (number of women in 5-year groups in 1945) was estimated by projecting backwards in time the number of women by age group—for instance, the number in the age group 30–35 in 1950 to the number in the age group 25–30 in 1945. The data for 1950 can be found in the "World Population Prospects: The 2017 Revision, File POP/7-3: Female population by five-year age group, region, subregion and country, 1950–2100 (thousands), United Nations Population Division, Department of Economic and Social Affairs" (https://population.un.org/wpp/). In this procedure, one needs to correct for mortality (which for adults is not very high). We estimated age-specific mortality by looking at the difference in numbers of women between 1950 and 1955. For instance, if the age group 25–29 in 1950 was 3% more than the age group 30–35 in 1955, we assumed that the age group 25–29 in 1945 would be 3% more than the age group 30–35 in 1950. On basis of our constructed 1945-estimates, we predicted 1940-estimates, going back In time to 1915.

The second (age-specific fertility) was estimated by the following procedure. We predicted age-specific fertility in 1950 on basis of age-specific fertility in 1955, and age-specific fertility in 1955 on

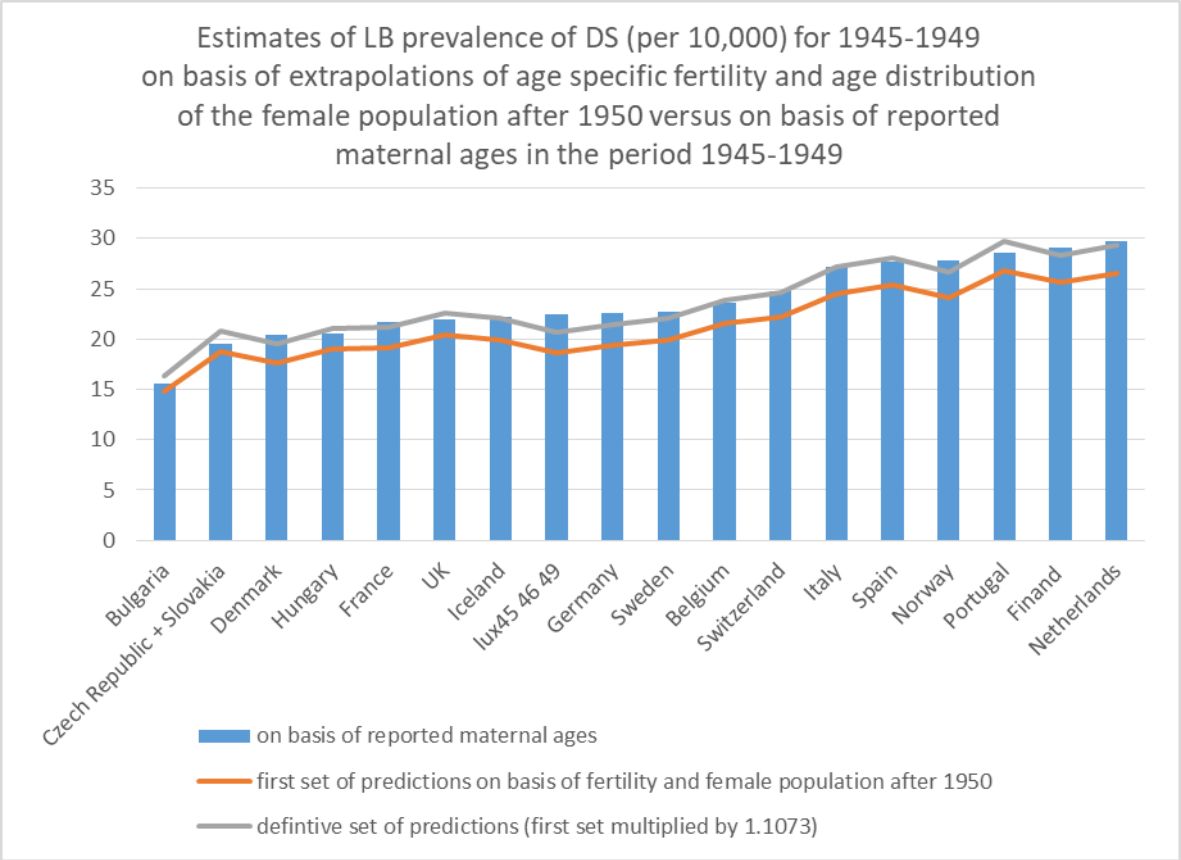
basis of the data from 1960, and in doing so, pooled these datasets together into one regression for each 5-year age group. The data for 1950, 1955, and 1960 can be found in "World Population Prospects: The 2017 Revision, File FERT/6: Births by five-year age group of mother, region, subregion and country, 1950-2100 (thousands)), United Nations Population Division, Department of Economic and Social Affairs" (https://population.un.org/wpp/). The best fitting regressions by age group (R^2 varying between 0.63 for 35–39 to 0.84 for 25–29 age group), we applied to the 1950-data to predict 1945 age-specific fertility rates. On basis of our 1945-estimates, we predicted 1940-estimates, going back in time to 1915.

By combining the estimated numbers of women by age group with the estimates of age-specific fertility rates, we predicted the number of LBs in the general population by maternal 5-year age group for 1915, 1920, 1925, 1930, 1935, 1940, and 1945. By applying the model of age-specific chance for a LB of a child with DS to these estimates, we predicted the LB prevalence of DS. Values for in-between years were interpolated. If predicted prevalence was higher than 33 per 10,000, we used 33 per 10,000 as value.

Validating the predictions

We compared the predicted numbers of LB prevalence of DS for the 5-year periods from 1935 and 1950 with reported numbers, if available (see section S3B).

For 1945–1949, the correlation between the estimates on basis of reported maternal ages and predicted numbers (on basis of age-specific fertility and age distribution of the female population in and after 1950) is high (correlation coefficient of 0.97), so higher values on basis of reported maternal ages are matched by higher predicted values (see Figure below). However, the predictions were on average 10% lower than the values on basis of reported maternal ages. As this seems to be a systematic deviation, we have made new—and definitive—predictions by multiplying the initial set with 1.1073.



For 1945–1949, we had data on maternal age distribution in general population for 19 European countries. For 16 countries the definitive predicted numbers were less than 5% different from the estimates on basis of reported maternal ages; for 3 countries between 5-10%. For 1945–1949, we had to use modeled estimates (on basis of age-specific fertility and female population in and after 1950) for 20 countries (as we could not find reported information on maternal age distribution for 1945-1949): Albania, Austria, Belarus, Bosnia and Herzegovina, Croatia, Estonia, Greece, Ireland, Latvia, Lithuania, Malta, Montenegro, North Macedonia, Poland, Republic of Moldova, Romania, Russian Federation, Serbia, Slovenia, and Ukraine.

For 1940–1944, correlation between values on basis of reported maternal ages and predicted values (on basis of age-specific fertility and age distribution of the female population in and after 1950) was 0.88. However, the predicted values were on average 8 percent too low. We multiplied our initial set of prediction with 1.0853 to construct our definitive predicted values. For this period, we had data on maternal age distribution in general population for 16 European countries. For 8 countries the predicted numbers were less than 5% different from the numbers on basis of reported maternal ages. For 7 countries, the difference was between 5–10%; for 1 country between 10–20%. For 1940–1944, we had to use modeled estimates (on basis of age-specific fertility and female population in and after 1950) for 23 countries: Albania, Austria, Belarus, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Germany, Greece, Hungary, Ireland, Latvia, Lithuania, Malta, Montenegro, North Macedonia, Poland, Republic of Moldova, Russian Federation, Serbia, Slovakia, Slovenia, and Ukraine.

For 1935–1939, correlation between values on basis of reported maternal ages and predicted values (on basis of age-specific fertility and age distribution of the female population in and after 1950) was 0.82. However, the predicted values were on average 9% too low. We multiplied our initial set of

prediction with 1.0997 to construct our definitive predicted values. For this period, we had data on maternal age distribution in general population for 21 European countries. For 12 countries the predicted numbers were less than 5% different from the numbers on basis of reported maternal ages. For 4 countries, the difference was between 5–10%, for 5 countries between 10–20%. For 1935–1939, we had to use modeled estimates (on basis of age-specific fertility and female population in and in and after 1950) for 18 countries: Albania, Austria, Belarus, Bosnia and Herzegovina, Croatia, Estonia, Ireland, Latvia, Lithuania, Malta, Montenegro, North Macedonia, Poland, Republic of Moldova, Russian Federation, Serbia, Slovenia, and Ukraine.

S3B. Sources for maternal age distribution before 1950

Western Europe

Austria – no info

Belgium
Years: 1939-1950
Source: DYB (Demographic Yearbook Collection of the United Nations (https://unstats.un.org/unsd/demographic-social/products/dyb/)

France
Years: 1936-1950; Source: DYB

Germany
Years: 1936-1938 and 1947-1948; Source: DYB

Luxembourg
Years: 1936-1950; Source: DYB

Netherlands
Years: 1963-1950;

Source National Office for Statistics, (in Dutch: Centraal Bureau voor de Statistiek). Table 'Birth; age mother (on 31-12), birth order and fertility rates 1950-2014; and 'Population, households and population dynamics, from 1899'
http://statline.cbs.nl/Statweb/publication/?DM=SLEN&PA=37744eng&D1=a&D2=0-35&D3=0,50,55,60,63-64&LA=EN&HDR=T&STB=G1,G2&VW=T; and
http://statline.cbs.nl/Statweb/publication/?DM=SLEN&PA=37556eng&D1=3-8,65-69,90-95,180,182-183,189-190&D2=37&LA=EN&VW=T retrieved 22-Nov-2018.

Switzerland
Years: 1936-1946 and 1948-1950; Source: DYB

Northern Europe

Denmark
Years: 1936-1950; Source: DYB

Estonia – no info

Finland
Years: 1936-1950; Source: DYB

Iceland
Years: 1936-1950; Source: DYB

Ireland – no info

Latvia – no info

Lithuania – no info

Norway
Years: 1936-1950; Source: DYB

Sweden
Years: 1936-1950; Source: DYB

United Kingdom
Years: 1938-1950
Source: England/Wales. Dataset Name: PBH31A Type of Dataset: Cross-sectional. Description: Live births: Age of mother in 5 year age-groups: within/outside marriage and sex 1938-2004 a. all live births and female births only. Birth Statistics : Historical Series of Statistics from Registrations of Births in England and Wales, 1837-1983. ONS (received by email from ONS in 2006);
Scotland: Table BT.2: Births, by mother's age, Scotland, 1945 to 2015 on https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/births/births-time-series-data (retrieved 22-Nov-2018); DYB for Scotland 1939-1944.

Southern Europe

Albania – no info

Bosnia and Herzegovina – no info

Croatia – no info

Greece
Years: 1936-1938; Source: DYB

Italy
Years: 1936-1943, 1945 and 1948-1950; Source DYB

Malta – no info

Montenegro – no info

North Macedonia – no info

Portugal
Years: 1936-1950; Source: DYB

Serbia (including Kosovo) – no info

Slovenia – no info

Spain
Years: 1936-1950; Source: DYB

Eastern Europe

Belarus – no info

Bulgaria
Years: 1938-1944 and 1949-1950; Source: DYB

Czech Republic (and Slovakia)
Years: 1936-1937 and 1949-1950; Source DYB

Hungary
Years: 1937-1938, 1945-1946 and 1948-1950; Source: DYB

Poland – no info

Republic of Moldova – no info

Romania
Years: 1936-1942; Source: DYB

Russian Federation – no info

Slovakia (and Czech Republic)
Years: 1936-1937 and 1949-1950; Source DYB

Ukraine – no info

S4. Modeling survival in DS

S4A. Constructing survival curves for DS

We adapted an earlier model from de Graaf et al. (2017a;b) (doi: 10.1002/ajmg.a.37001 and doi: 10.1002/ajmg.a.38402). On the basis of multiple historical studies on the survival in persons with DS in developed countries, de Graaf et al. (2017a) constructed and validated a model with different survival curves for people with DS for each year of birth, and the authors applied this model to the U.S. In addition, they constructed separate curves for different ethnic groups in the U.S., based on the relationship between 1-year survival in these ethnic groups in general population and the 1-year survival in people with DS during the period 1983–2003. De Graaf et al. (2017a) extrapolated this relation back in time. In constructing 1-year survival in children with DS, de Graaf et al. (2017b) used the same strategy to take into account historical differences in 1-year mortality rates in the general population between U.S. states.

Constructing 1-year survival rates for DS

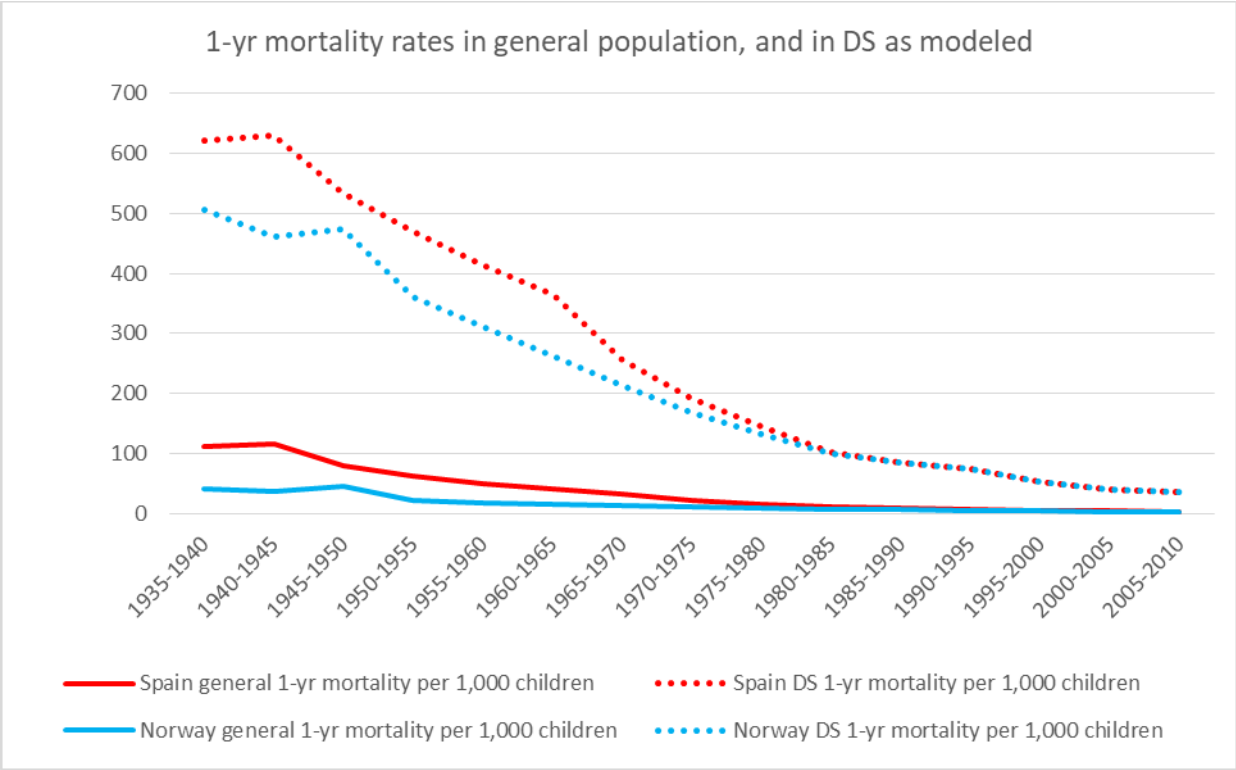
In our European study, we have assumed that a lower 1-year survival in the general population (see S4B for sources) will be indicative for a less well-developed medical care system, which will concomitantly impact the survival of children with DS. We used a similar strategy as de Graaf et al. (2017a;b) to correct for this probable effect of less developed medical care, linked to lower survival in general population. It should be noted that we have not corrected for a possible better survival of children with DS than was constructed for the U.S. The U.S. model estimates were based on studies from diverse developed Western countries and, as such, were not specific for the U.S. only. So, if the general 1-year mortality in a specific year was lower than the 1-year mortality in general U.S. population, we have applied the 1-year survival for children with DS as constructed by de Graaf et al. (2017a) for the U.S.

However, we wanted to correct for situations in which a country had a clearly higher 1-year mortality in the general population than did the U.S. If the 1-year general mortality in a country for a specific year was between the 1-year general mortality (for all ethnic groups taken together) for the same year in the U.S. and the 1-year mortality for non-Hispanic Blacks (NHB), we assumed that the 1-year mortality *for children with DS* in that country also had a similar in-between value. So, if the value of 1-year mortality in the general population in a country would be at a quarter of the distance between the corresponding U.S. value for the general population and the U.S. value for NHB, we would assign a value to that country's 1-year survival *of children with DS* at a quarter of the distance between the U.S. value *for DS* in general population and the U.S. value *for DS* in NHB (values for mortality in DS as constructed by de Graaf et al., 2017a).

If a country's 1-year mortality in the general population was higher than the 1-year mortality in NHB in the U.S., we used a different strategy. We have plotted the values of 1-year mortality estimates in U.S. NHB with DS against the general 1-year mortality in U.S. for NHB for the period 1955–2010. When the general mortality < 32 per 1,000 deaths in general NHB population, a linear regression fitted the data well (R^2 = 0.95). We have used this regression to predict 1-year mortality *in DS* on basis of 1-year mortality in the general population in European countries, if the 1-year mortality in the general population in a specific country was higher than the 1-year mortality in NHB in the U.S. and < 32 per 1,000 deaths. When the general mortality > 32 per 1,000 deaths, this linear prediction overestimates the values for DS, and logarithmic regression fit the data better (R^2 = 0.96). We used this equation to predict 1-year survival in DS, if the 1-year mortality in general population in a specific country was higher than the 1-year mortality in NHB in the US and $\geq$ 32 per 1,000 deaths.

Finally, to set a limit, we have decided that if the procedures led to an estimate of 1-year mortality for DS higher than 800 per 1,000 LBs, we keep the value at 800.

To illustrate the effect of the procedure above, we present in the graph below the 1-year mortality rates in general population and our constructed 1-year mortality rates in DS for two European countries.



As the data on 1-year mortality for the general population are available by 5-year groupings (1950–1955, 1955–1960, etc.), we have decided to assign the value for survival in people with DS to the midpoint of the range of years (i.e., 1952, 1957, etc.), and to interpolate the values for in-between years.

Constructing 5- and 10-year survival rates for children with DS

We fitted a linear relation between 1-year survival in DS and 5-year survival in DS and between 1-year survival in DS and 10-year survival in DS, on basis of the rates found in the multiple historical studies about the survival in persons with DS in developed countries, as reported by de Graaf et al. (2017a.) We used these equations to predict 5-year survival and 10-year survival in our European countries on basis of the estimates we made for 1-year survival rates in DS.

Survival beyond 10 years of age

For modeling survival rates beyond 10 years of age, de Graaf et al. (2017a) made use of survival curves for DS from 7 different historical studies. The survival curves beyond 10 years of age from these studies were highly similar. As such, we made use of the average of these curves. For the period before 1950, de Graaf et al. (2017a) used a survival curve beyond 10 years of age with a more rapid decrease, based on the work of Penrose (1949) (J. Ment. Sci. 95, 685–688). De Graaf et al. used this more hazardous survival curve for predicting the survival of cohorts born before 1940 until the calendar year 1950. In 1950, 60% of children with DS in the U.S. were estimated to survive their first year of live. If in a country, the estimated 1-year survival rate for DS was <60%, we have assumed

that survival beyond 10 years of age in earlier cohorts followed the more hazardous survival age up to that year.

Adjusting for Germany and Austria for years of birth before 1945
For Germany and Austria, we made an additional assumption that people with DS born before 1945 had a much lower survival than we had modeled for other (Western) countries. Historical records show that the Nazis systematically killed people with disabilities in Germany and Austria. We assumed that half of the birth cohorts before 1945 were killed. However, these persons with DS would be 70+ years old in 2015, which already is a small group.

Applying survival curves to estimates of number of actual births of children with DS
We applied our constructed survival curves by year to the estimated numbers of LBs of children with DS by year to predict the number, by age group, of people with DS alive in the population for different years in the period 1950–2015.
For further validation of the model, we also predicted the number of deaths of people with DS by age group for different years.

Validating and adjusting the survival modeling
We utilized two ways of validating and, if necessary, readjusting the model. First, there are a few studies in which the number of people with DS by age group has been estimated using counts in population. We compared these counts with our modeled predictions. Secondly, we compared our age distribution of deaths of people with DS for certain years with information on this age distribution from national statistical offices.

In S5, we explain the results of this validation approach, which has led us to adjust our estimates for survival for former East bloc countries (which will be explained in S5).

S4B. Sources for infant mortality in general population

In building our model, we have used data on 1-year survival in general population for the different European countries. For 1950–2015, these data are available from the United Nations in File MORT/1-1: Infant mortality rate (both sexes combined) by region, subregion and country, 1950–2100 (infant deaths per 1,000 live births) in the World Population Prospects of the United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, DVD Edition.
https://population.un.org/wpp/DVD/Files/1_Indicators%20(Standard)/EXCEL_FILES/3_Mortality/WPP2017_MORT_F01_1_IMR_BOTH_SEXES.xlsx (Accessed November 9, 2018).

For the period 1900–1950, data on 1-year mortality rates in 20 European countries (Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Spain, Sweden, Switzerland, United Kingdom) at
https://www.gapminder.org/data/ (accessed October 8, 2019)
For 1900–1910; 1925–1930; 1935–1950, for Russia: Kumo, K., Morinaga, T., Shida, Y. (2007). Long-Term Population Statistics for Russia 1867-2002. The Institute of Economic Research. Hitotsubashi University. Kunitachi, Tokyo, Japan.
For 1920–1950 in Latvia: https://en.wikipedia.org/wiki/Demographics_of_Latvia#Vital_statistics (accessed October 6, 2019)

We have used these data to predict the 1-year mortality before 1950 for other countries as well, by looking which equation predicts best the relation between 1-year survival in 1950–1955 with that in 1945–1950, and between 1950–1955 and 1940–1945, etc. These equations were applied to the 1-year mortality rates of 1950–1955 to estimate these for the earlier 5-year periods. For the 22 countries with data (see above), we have used these reported data in modeling. For the other countries, we have used the procedure described above.

S5. Validating and adjusting the model

S5A. Comparison with population counts of people with DS

When validating our approach, we found out that our model had a reasonable fit with empirical data from population counts of people with DS (and with the age distribution of age at death) in countries that are not from the former East bloc (we refer to European countries that were not formerly under communism as "former West bloc countries"). However, the modeled historical survival rates appear to need adjustment for countries from the former East bloc. Therefore, in this supplemental section, we present the results for former West bloc countries and for former East bloc countries separately.

Countries from the former West bloc

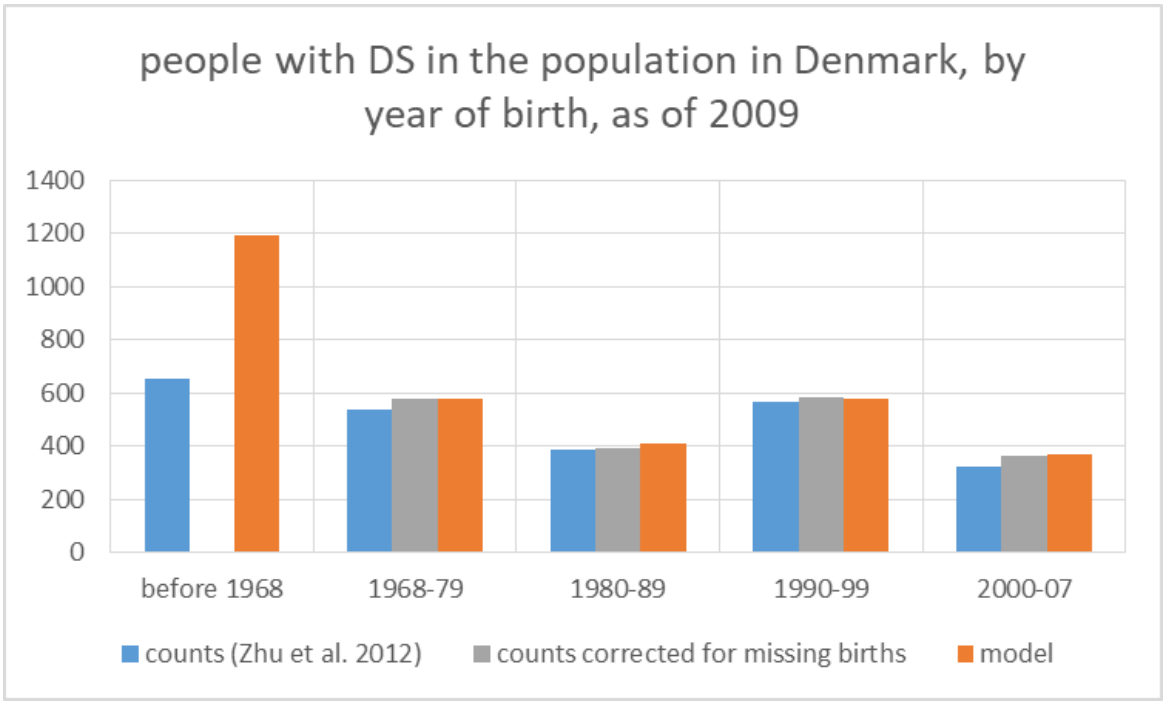
We found information on population counts of people with DS for four different countries. Below, we discuss the results from Denmark, Finland, Spain, and the United Kingdom, respectively.

Denmark

Counts of people with DS (alive in the population as of 2009) can be based on the following study:

Zhu et al. (2007). Survival among people with Down syndrome: A nationwide population-based study in Denmark. *Genetics in Medicine*: 15(1):64-69. DOI: 10.1038/gim.2012.93.

Zhu et al. used information from the Danish Cytogenetic Register, which was founded in 1968. It is expected that all or almost all children with DS born after 1968 are included in the Register. The register also retrospectively collected data on all analyses performed since the introduction of the cytogenetic analyses in 1961. However, people with DS born before 1968 may not always have been karyotyped. (We expect that the karyotyping of people with DS born before 1968 was gradual in adoption. To draw upon a comparison, in the Netherlands from 1991–1995, out of 1,191 postnatal cytogenetic diagnoses of DS, 348 (29%) were of adults who were karyotyped for the first time. We would expect the same kind of slow adoption in Denmark, which implies that many of the people of DS born before 1968 would never have been karyotyped before their death.)



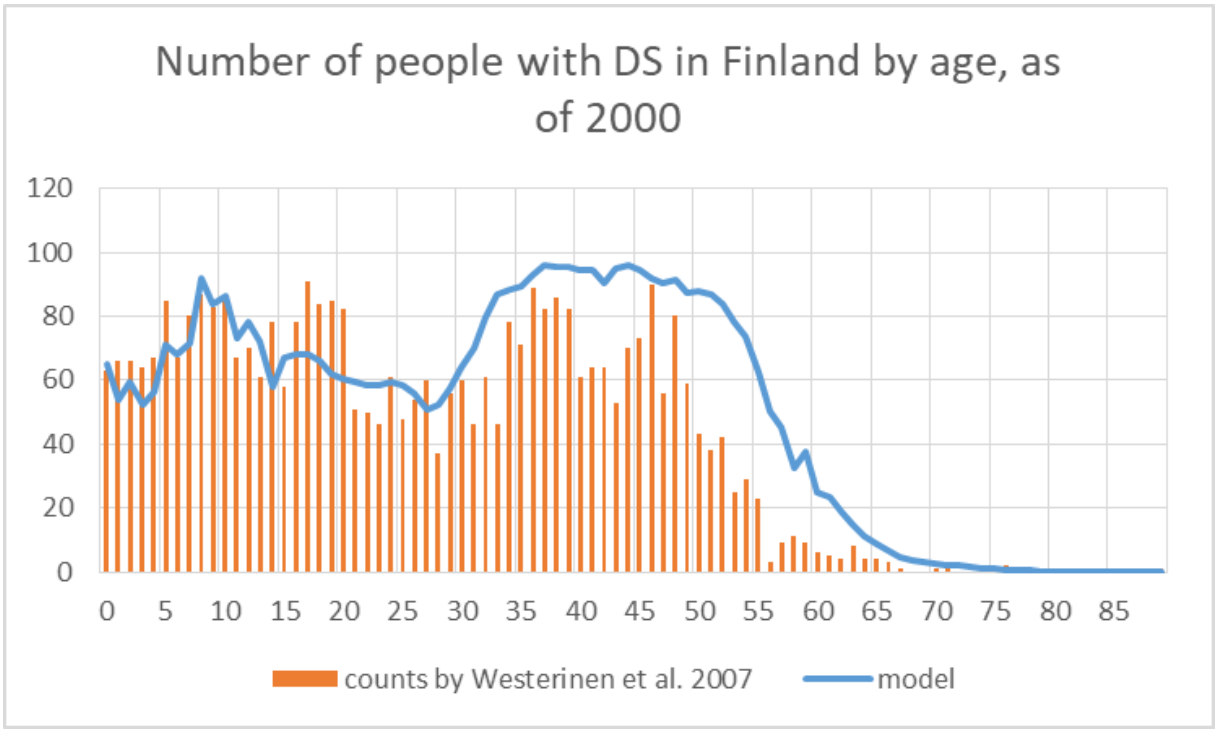
We corrected the counts for the period 1968–2007 for missing births since our primary sources (Aarhus University Hospital; see S1D) reported slightly higher numbers of LBs of children with DS than those in Zhu et al. Our model's predictions for the years of birth 1968–79, 1980–89, 1990–99, and 2000–07 match these corrected counts, which shows that the survival of people with DS born after 1968 is modeled adequately. In comparison to the counts by Zhu et al., the model predicts a far higher number alive in 2007 from the years of birth before 1968 (652 versus 1,192, or 1.83 times higher). However, as explained above, it is uncertain if all elderly people with DS are karyotyped. Under-ascertainment of people born before 1968 might explain the discrepancy between counts and the model.

Alternatively, mortality may have been higher than modeled. Based on Zhu et al., in April 1968, 1,266 people with DS born before 1968 were alive. Our model predicts 2,346 people alive in 1968 and born before 1968 (that is, 1.85 times as high). According to Zhu et al., 52% of people alive in 1968 were still alive in 2009; our model predicts a comparable 51%. So, survival after 1968 in the model and in the study of Zhu et al. is highly similar. Survival before 1968 may have been less favorable than modeled. However, in regards to Denmark, a highly developed country, we would not expect such a lower survival. The model for the UK (see below) fits well for the UK-based counts of Alexander et al. (2016), even for the older age groups (born before 1968). Historically, the survival of young children (under 1 year of age mortality) in the general population (which we consider to be an indicator for the quality of health care) is highly similar between Denmark and the UK. Thus, we would not expect the survival of children with DS before 1968 to be far worse in Denmark than in the UK.

Finland

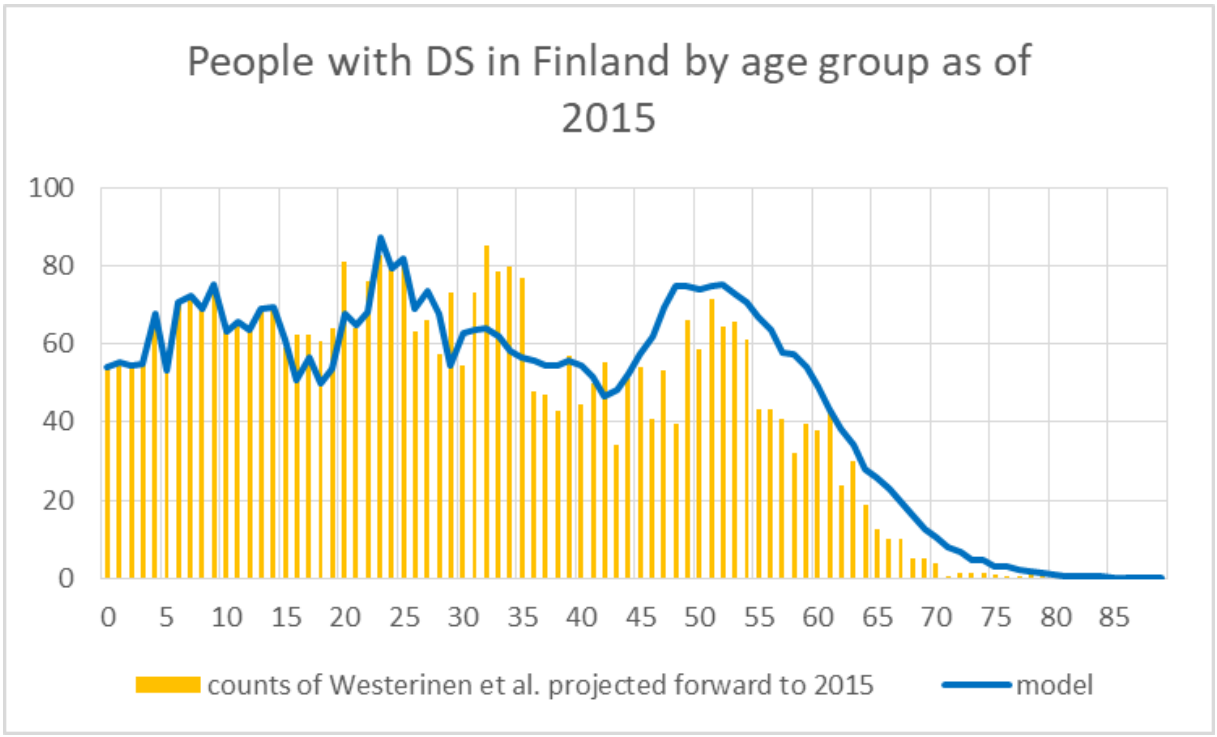
In the graph below, the counts are from unpublished results (received by e-mail from H. Westerinen on March 29, 2019) from this study:

Westerinen H., Kaski M., Virta L., Almqvist F., Iivanainen M. (2007). Prevalence of intellectual disability: a comprehensive study based on national registers. *Journal of Intellectual Disability Research* 51(9): 715-25.



The counts were based on combining multiple registers. Population prevalence, as of 2000, on the basis of the counts by Westerinen et al. (2007) would be 7.1 per 10,000 inhabitants, compared to 8.7 per 10,000 from our model. However, as can be seen from the graph above, counts and modeled estimates are similar for the younger age groups, but differ for ages > 35 and especially for ages > 50. This discrepancy might be the result of under-ascertainment in the counts. It is possible that in the registers for people with a disability, the diagnosis DS is not always reported, especially for older age groups. Alternatively, survival may have been lower in Finland before 1965, and especially before 1950, than the model assumes. However, Finland being a highly developed country, we would not expect such a lower survival. As said, the model for the UK fits well for the UK-based counts of Alexander et al. (2016), even for the older age groups (see below). Historically, the survival of young children (under 1 year of age mortality) in the general population (which we consider to be an indicator for health care) is highly similar in Finland and the UK.

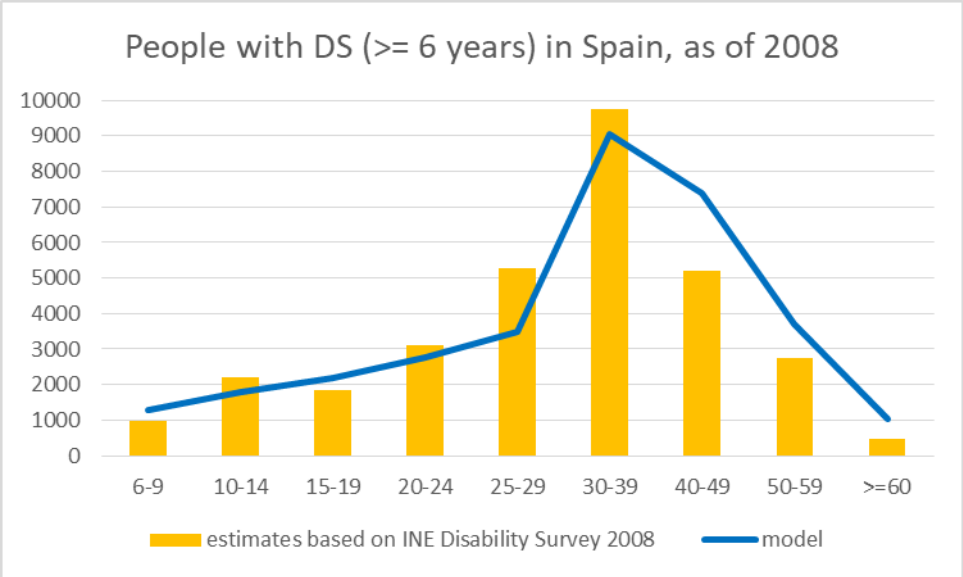
If we take the Finland counts from 2000 as the starting point, and apply the age-specific survival of the model between 2000 to 2015 to the numbers counted in 2000 (adding the ones born after 2000 on basis of the model), population prevalence on basis of these forward projected counts would be 7.0 per 10,000 inhabitants as of 2015, compared to 7.5 per 10,000 on basis of our model. See the graph below for the age distribution.



Spain

In 2008, the National Statistics Institute (INE) conducted a survey in Spain on Disabilities: The Disabilities, Independence and Dependency Situations Survey (DIDSS). A total number of 96,075 households were interviewed, using a stratified two-stage sampling procedure. Applying a weighting procedure to make the numbers representative for all Spanish households, the number of people who were six years of age and older were estimated by different types of disability. On basis of the number of people in the households surveyed, INE estimated there were 31,545 people with DS who were 6 years and older living in Spanish households. We estimated a corresponding 95%-confidence interval of 25,994 to 37,099, using the method described by DIDSS (http://www.ine.es/en/metodologia/t15/t1530418_en.pdf; accessed August 9, 2019). Our model

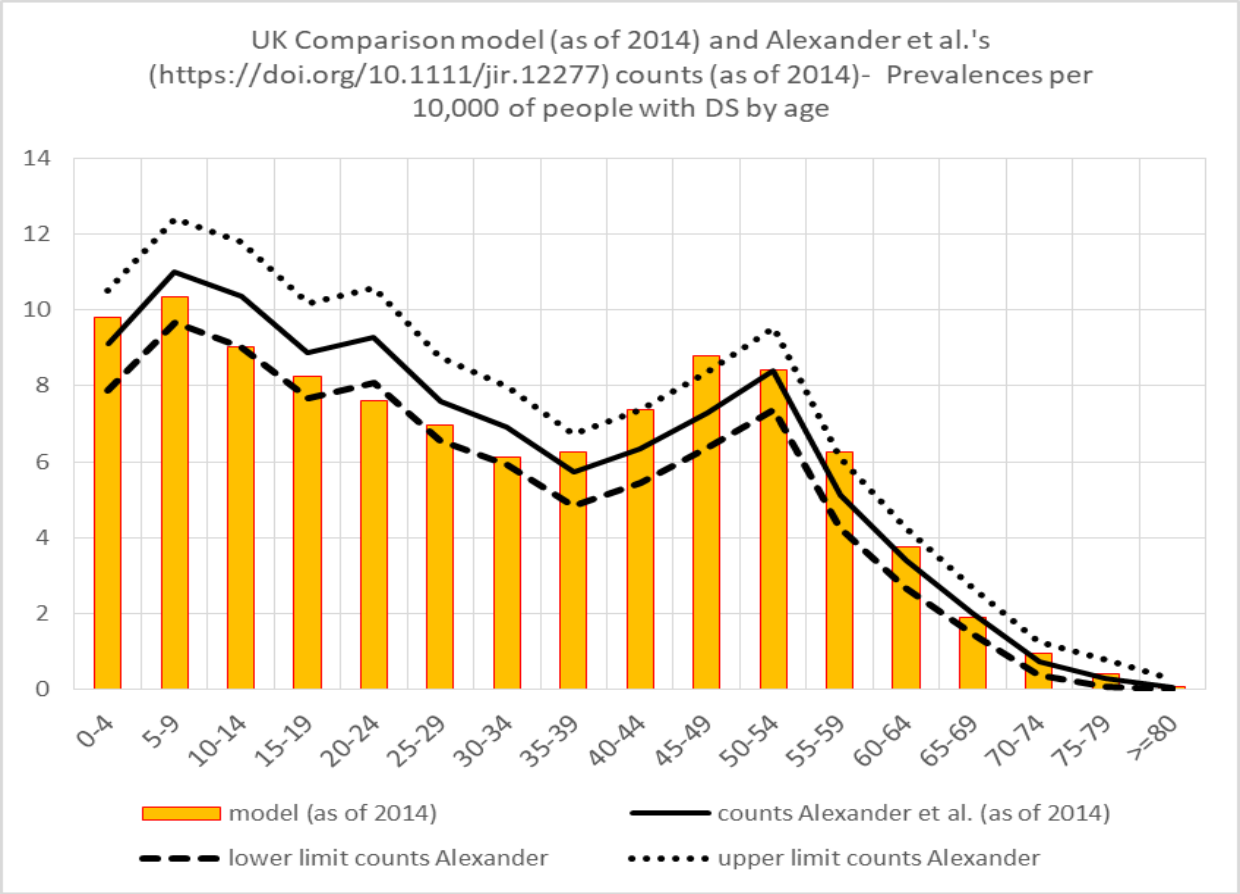
predicts 32,708 people with DS who are 6 years and older in Spain, which is 1,164 persons more (only 4% higher) than the survey's estimate, but well inside the confidence interval.



Subsequently, we used the microdata from the survey (http://www.ine.es/dyngs/INEbase/en/operacion.htm?c=Estadistica_C&cid=1254736176782&menu=resultados&secc=1254736195313&idp=1254735573175; accessed August 9, 2019) to divide the total number by age group (see the Figure above). Survey and modeled estimates show a similar age distribution; however, there are some differences. There appears to be a pronounced difference in the numbers estimated above 40 years of age, which are lower according to the Survey. However, INE warns that data corresponding to cells with fewer than 5,000 persons should be viewed with caution because they may be affected by large sampling errors. In addition, there might be a systematic reason why the Survey numbers are lower above 40 years of age. People living in collective establishments (e.g., institutions for the elderly or for persons with disabilities) were not counted in the Survey for households. In an additional Survey (the Disabilities, Independence and Dependency Situations Survey - Centres (DIDSSc)), the number of persons with disabilities (≥6 years of age) who were residents in Spanish centers for elderly persons, center for persons with disabilities, psychiatric hospitals, and geriatric hospitals, were estimated. For DS, this number was estimated at 2,500. We assume that people with DS would more often live in such an institution if they were older and that a relative large proportion of these additional 2,500 persons would add up to the numbers above 40 years of age.

United Kingdom

Alexander et al. (2016) estimated the prevalence of DS in the UK general population as of 2014 by age group (and sex) using a large primary care database containing information on 2,476 individuals with DS in a total of 3,899,513 individuals enrolled, belonging to 684 UK primary care practices. According to Alexander et al., as the general practitioner in the UK acts as the gatekeeper of access to healthcare, this specific database, The Clinical Practice Research Datalink (CPRD), is broadly representative of the UK population. Alexander et al. (2016) estimated that 6.35 people with DS alive per 10,000 people in the UK as of 2014; our model predicts 6.44 per 10,000 for the same year. The age distribution is fairly similar, as can be seen in the graph below. Most of the values predicted by the model are inside the 95% Confidence Interval as estimated by Alexander et al. (2016).



Counts are from Alexander, M., Ding, Y., Foskett, N., Petri, H., Wandel, C. & Khwaja, O. (2016). Population prevalence of Down's syndrome in the United Kingdom. *Journal of Intellectual Disability Research* 20;60(9): 874-8. doi: 10.1111/jir.12277. Epub 2016 Mar 28.

Countries from the former East bloc

We found information on population counts of people with DS for four different countries. Below, we will discuss the results from Albania, Croatia, Romania, and Ukraine, respectively.

Albania

In the Table below, we reprint the numbers of people with DS in Albania as registered by the National Social Service, an agency of the Ministry of Welfare and Social Protection. Column A shows the numbers registered in 2019. Column B is a projection of the numbers in A back in time to 2015 on the basis of our modeled survival between 2015–2019. Column C is the number as registered by the National Social Service in 2015.

We expect for 2015–19, that survival in Albania is not extraordinary unfavorable and would be comparable to Western European countries, with a small correction in the childhood survival of children with DS on basis of the less favorable 1-year survival in the general population of Albania (see S4A).

Year of birth	A. People with DS registered in 2019	B. Probably alive in 2015 (on basis of the ones registered in 2019 and applying the Western European survival model)	C. Registered in 2015
≥2016	41	0	0
2011–2015	86	89	35
2006–2010	92	93	90
2001–2005	83	84	85
1996–2000	86	87	75
1991–1995	68	69	73
1986–1990	46	47	48
1981–1985	52	53	61
1976–1980	41	42	48
1971–1975	36	38	48
1966–1970	20	22	28
1961–1965	20	24	25
≤ 1960	10	15	18
Total	681	664	634

For most years of birth, Column C more or less equals Colum B. If the number in 2015 (Column C) is larger than Column B, then probably survival between 2015 and 2019 was a bit less favorable than modeled. If the number in 2015 (Column C) is smaller than Column B, especially if Column C is also smaller than Column A, then there was under-registration in 2015. This is clearly the case for the years of birth 2011–15 (only 39% of Column B is registered in Column C). For the older age groups, there is only some indication of undercounting as of 2015—i.e., for the years of birth 1996–2000 (86% of Column B seems to be registered in Column C) of and for 2006–2010 (96%).

We have complete information on the number of LBs with DS in Albania for 2011–15 (see S1D)—i.e., 157 children with DS. If we apply our modeled survival rates on this number, this yields an estimated 130 of these children still alive in 2015. As we can see in the Table above, only 89 are registered in Column B, which is 68%. We assumed that this might be due to under-ascertainment and that this level of under-ascertainment will also apply to the older age groups. (However, it could (partly) be a result of a higher mortality than modeled, too).

In the Table below, you find the number of people with DS probably alive in 2015 based on the registration of the National Social Service as of 2019 (Column D), and these numbers corrected for under-ascertainment (Column E), assuming that 68% of the actual people alive were registered.

Column F is the modeled number after applying to our estimates of LBs with DS the survival rates, modeled like in Western Europe, with only small adaptations in survival in DS to take into account differences in 1-year survival in general population (see S4A). As we can see, these numbers (Column F) are much higher than what we would expect on basis of Column E.

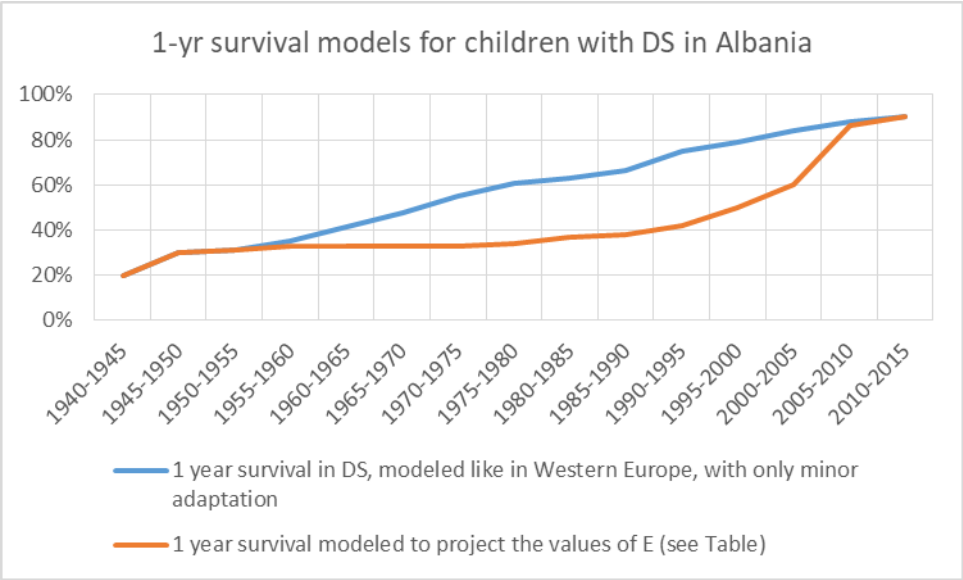
This implies that there might be severe under-ascertainment in the register. However, we would not expect such severe under-ascertainment, as there is a strong financial incentive to register—i.e., the state pays to each individual with DS a monthly support fee ($75) (personal e-mail by Emanuela Zaimi of Down Syndrome Albania Foundation (DSA) & Achievement and Development Center, August 15, 2017). Zaimi explains that in a poor country like Albania, every family needs this money. Of course, there might be some under-ascertainment, as not all families are aware of their rights.

Year of birth	D. People with DS probably alive in 2015 (on basis of the ones registered in 2019 and survival model)	E. People with DS probably alive in 2015, after correcting for under registration	F. People with DS modeled as being alive in 2015 if we model survival like in Western Europe	G. People with DS modeled as being alive in 2015 if we try to fit the survival to yield numbers similar to E
2011–2015	89	131	137	135
2006–2010	93	137	157	150
2001–2005	84	123	202	146
1996–2000	87	128	260	134
1991–1995	69	101	292	121
1986–1990	47	68	305	103
1981–1985	53	77	286	77
1976–1980	42	62	277	62
1971–1975	38	56	275	57
1966–1970	22	32	233	48
1961–1965	24	35	162	31
≤ 1960	15	22	107	22
Total	664	971	2693	1086

The alternative explanation would be that survival in the past has been much poorer than we had modeled initially. There are certainly reasons to assume this might be the case. In Western European countries, children with DS with a heart condition are diagnosed as such, and, if needed, a heart operation is performed, often at a very young age, with a high success rate. This has contributed to more favorable survival outcomes in DS. Screening for heart conditions in neonates with DS, and operating in the first months of life, has been normal since the early 1990s. In contrast, according to Zaimi (e-mail July 14, 2017), in Albania it is only since 2007 that every child with DS has had his or her heart checked after birth, and complicated operations are still not possible in Albania. According to Zaimi, in Albania, perhaps even up to 2010, there was a lack of quality medical care for individuals with DS and a lack of awareness of their rights and needs, which might explain higher mortality rates. Before 1990, the care for people with DS (or other developmental disabilities) in Albania may have been extremely poor (https://www.theguardian.com/news/2014/dec/10/-sp-ceausescus-children; accessed September 12, 2019).

Assuming that survival may have been poorer than we had modeled, we reversed our procedure—i.e., we have tried to model the 1-year survival rates for children with DS (which is the starting point for modeling survival at higher ages, too) in such a way that the adapted model projects numbers (Column G) that are in line with Column E. The match is not perfect, but numbers in Column G do resemble numbers in Column E better than the initial model.

The Figure below shows that the initial model had an increase in 1-year survival rates for the whole period, 1940 to 2015. The adapted model shows very little increase from 1955 to 1990, followed by a rapid increase in recent years. It should be understood that adapting the 1-year survival rates in the model also affects the modeled 5- and 10-year survival rates, as these are predicted on basis of the 1-year survival rates (see S4A) and affects the survival rates above 10 years of age, as we have assumed a poorer survival of older cohorts above 10 years of age if the modeled 1-year survival rates were lower than 60% (see S4D).



Croatia

In the Table below, we report the number of people with DS probably alive in 2015, based on the registration by the Croatian Institute of Public Health as of 2018 (Column A) (see S1C). Column B is the modeled number of people with DS after applying survival rates to our modeled number of LBs with DS. Survival (for Column B) is modeled like in Western Europe (see S4A). As we can see, before 2000, these numbers (Column B) are much higher than what we would expect on basis of Column A.

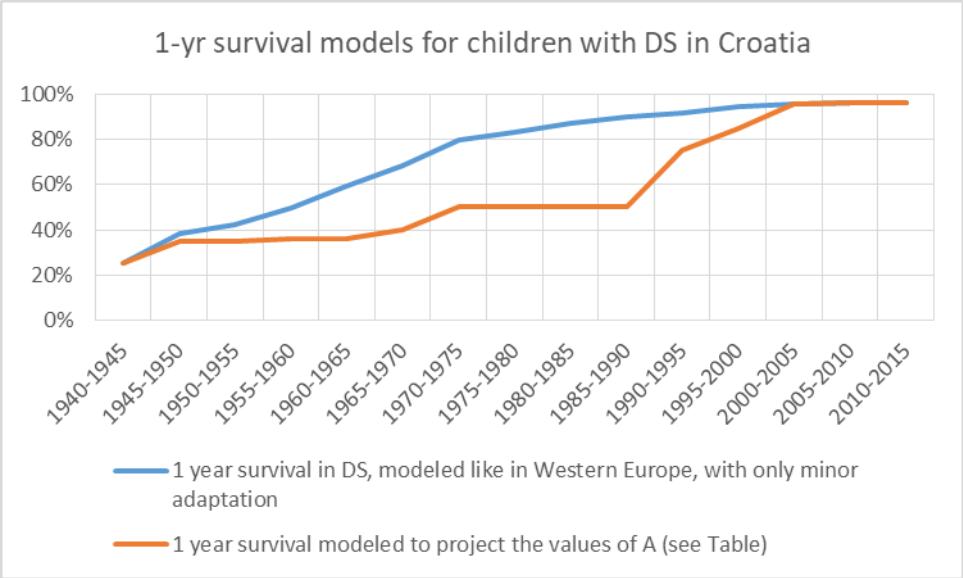
That implies there might be severe under-ascertainment in the register for years of birth before 2000. However, we would not expect such severe under-ascertainment, as there is a strong financial incentive to register—i.e., the state pays to each individual with DS a monthly support, and this is an important reason for families to register. Additionally, persons who are in institutions have to go on occasion to the Center for Social Welfare and are registered there, as well (personal e-mail by Dinka Vukovic of Croatia Down Syndrome Association, July 13, 2017). Only in very young children, there is a good explanation for under-ascertainment, because the registering process takes some time. This is reflected by the data for 2011–15 (as 2014 and 2015 are not yet complete).

Year of birth	A. People with DS probably alive in 2015 (on basis of the ones registered in 2019 and survival model)	B. People with DS modeled as being alive in 2015 if we model survival like in Western Europe	C. People with DS modeled as being alive in 2015 if we try to fit the survival to yield numbers similar to B
2011–2015	191	234	234
2006–2010	240	240	238
2001–2005	229	234	228
1996–2000	235	258	232
1991–1995	178	228	170
1986–1990	133	257	139
1981–1985	108	275	117
1976–1980	107	281	116
1971–1975	109	262	92
1966–1970	54	226	65
1961–1965	67	182	45
1956–1960	29	126	30
1951–1955	15	71	15
≤ 1950	5	32	6
Total	1700	2905	1726

The alternative explanation would be that survival before 2000 had been much poorer than we have modeled. Again, there are certainly reasons to assume this might be the case. In Western European countries, children with DS with a heart condition are diagnosed as such, and, if needed, a heart operation is performed, often at a very young age, with a high success rate. This has contributed to more favorable survival outcomes in DS. Screening for heart conditions in neonates with DS, and operating in the first months of life has been normal since the early 1990s. In contrast, according to Vukovic (e-mail July 13, 2017), in Croatia before 2000, if a child had a severe heart problem, it was not yet possible to operate in Croatia. The neonate had to be sent abroad for an operation. Before 1990, under communist rule, the medical care for children with DS may have been even poorer.

Assuming that survival before 2000 may have been poorer than we had modeled, we reversed our procedure—i.e., we have tried to model the 1-year survival rates for children with DS (which is the starting point for modeling survival at higher ages, too) in such a way that the adapted model projects numbers (Column C) that are in line with Column A. The match is not perfect, but numbers in Column C do resemble numbers in Column A far better than the initial model.

The Figure below shows that the initial model had an increase in 1-year survival rates for the whole period 1940 to 2015. The adapted model shows relatively little increase from 1955 to 1990, followed by a rapid increase in recent years.



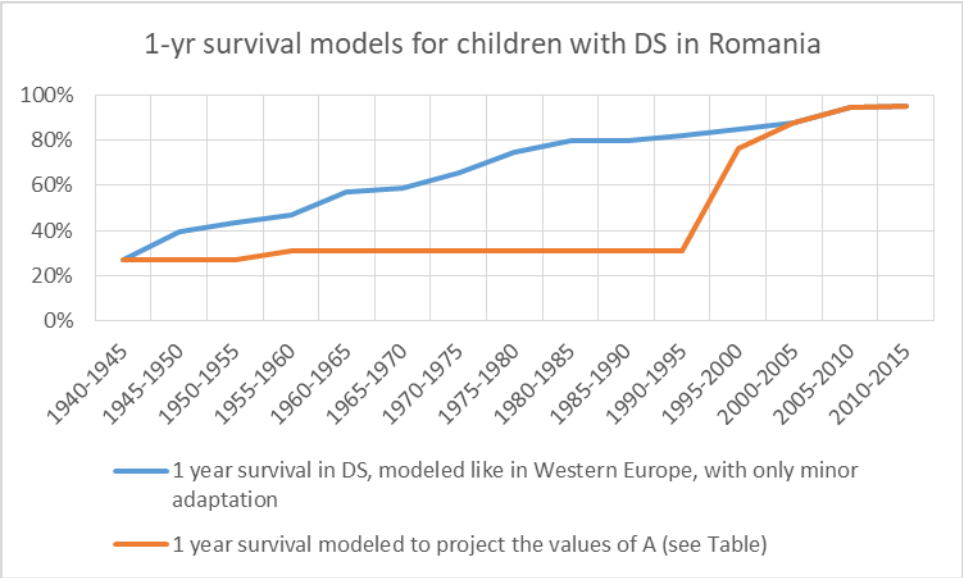
Romania

Maria Madalina Turza of the European Centre for the Rights of Children with Disabilities (CEDC) provided data on people with DS alive in Romania (personal e-mail, August 3, 2017). In late 2015, the CEDCD requested information about the number of people with DS from all 46 General Directorates of Social Assistance and Child Protection (DGASPC) in Romania. At that time, there were 3,741 people with DS registered with the authorities in Romania (except for Ilfov County which failed to answer, but has less than 2% of the Romanian general population).

In the Table below, we present the numbers by age group (Column A) and compare these with the projections of the initial model (Column B). It is clear that the modeled numbers are much higher. In Croatia and Albania, we found clear under-ascertainment in the youngest age groups, as not all children with DS are registered immediately. It is also possible that registration is incomplete in older age groups. We used the 3–6 year age group (years of birth ~2009–2012) to estimate possible undercounting, as within this age group families probably had enough time to register their child. We also expect survival from 2009 onwards to be adequately modeled by the initial model. For this age group, the model projects 1.5 times as many children than those registered. We assumed that this is a result of under-ascertainment in the registered numbers, and we have assumed that this magnitude of under-ascertainment will also occur in the other age groups. In Column C, the numbers corrected for this possible under-ascertainment are presented. Subsequently, we have followed the same procedure as we had done in Croatia and Albania—that is, adapting our modeled 1-year survival rates for DS (and thereby the corresponding 5- and 10-year survival rates) in such a way that the model produces numbers (Column D) that are more or less similar to the numbers in Column C.

Year of birth	A. People with DS registered by the end of 2015	B. People with DS modeled as being alive in 2015 if we model survival like in Western Europe	C. People with DS registered by the end of 2015, after correcting for possible under-ascertainment	D. People with DS modeled as being alive in 2015 if we try to fit the survival to yield numbers similar to C
2013–2015	363	618	545	618
2009–2012	592	889	889	889
2002–2008	1037	1548	1557	1522
1998–2001	649	855	974	768
1985–1997	500	3225	751	969
1965–1984	534	5535	802	736
1935–1964	64	1531	96	166
≤ 1934	2	29	3	6
Total	3741	14230	5617	5674

The Figure below shows that the initial model had an increase in 1-year survival rates for the whole period of 1940 to 2015. The adapted model shows no increase from 1955 to 1990, followed by a rapid increase in recent years.



Ukraine

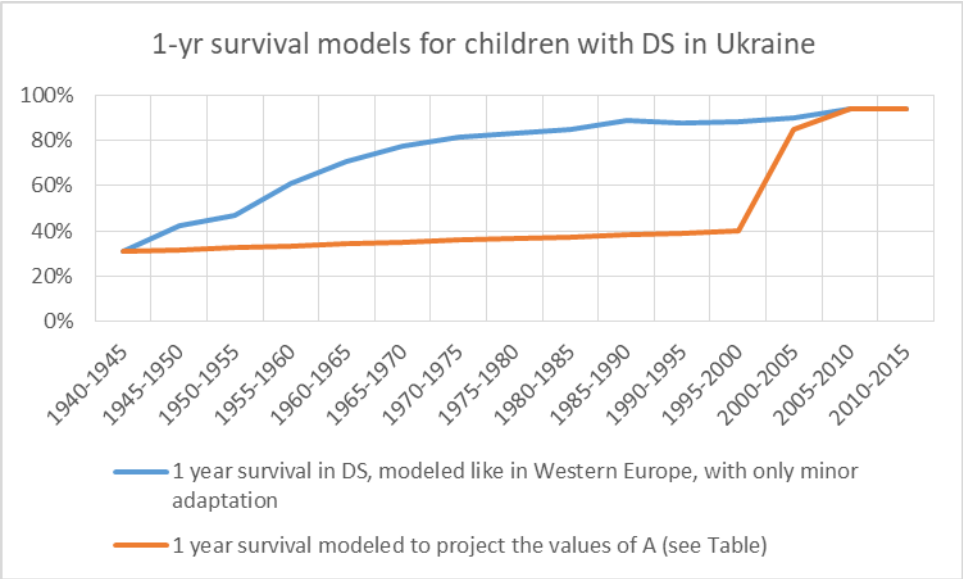
Sergey Kuryanov, President of the Ukrainian Charitable Organization "Down Syndrome," provided data on people with DS in the age range 0–17 (personal e-mail, July 18, 2017). The Center of Medical Statistic of the Ministry of Health protection of Ukraine provided these numbers to Sergey Kuryanov. During 2014, there were 4,063 children (ages 0-17) in Ukraine who had the status of “disabled" due to DS. No data are available for people with DS who are 18 years or older.

In the Table below, we present the numbers by age group (Column A) and compare these with the projections of the initial model (Column B). We have used the 3–6 years old age group (years of birth

~2008–2011) to estimate possible undercounting, as for that age group families probably had enough time to register their child. We also expect survival from 2008 onwards to be adequately modeled by the initial model. For this age group, the model projects 1.77 times as many children than those registered. We have assumed that this is a result of under-ascertainment in the registered numbers, and we have assumed that this magnitude of under-ascertainment will also occur in the other age groups. In Column C, the numbers corrected for this possible under-ascertainment are presented. Subsequently, we followed the same procedure that we used with Croatia, Albania, and Romania—that is, adapting our modeled 1-year survival rates for DS (and thereby the corresponding 5- and 10-year survival rates) in such a way that the model produces numbers (Column D) that are more or less similar to the numbers in Column C. For survival rates for 1950–1996, we extrapolated between the value of the initial model for 1940–1945 to the adapted value for 1995–2000.

Year of birth	A. People with DS registered in 2014	B. People with DS modeled as being alive in 2014 if we model survival like in Western Europe	C. People with DS registered in 2014, after correcting for possible under-ascertainment	D. People with DS modeled as being alive in 2015 if we try to fit the survival to yield numbers similar to C
2012–2014	857	1751	1514	1751
2008–2011	1248	2205	2205	2199
2000–2007	1649	3340	2914	2828
1997–1999	309	1138	546	574
Total	4063	8434	7179	7352

The Figure below shows that the initial model had an increase in 1-year survival rates for the whole period of 1940 to 2015. The adapted model shows no increase from 1950 to 1995, followed by a rapid increase in recent years.



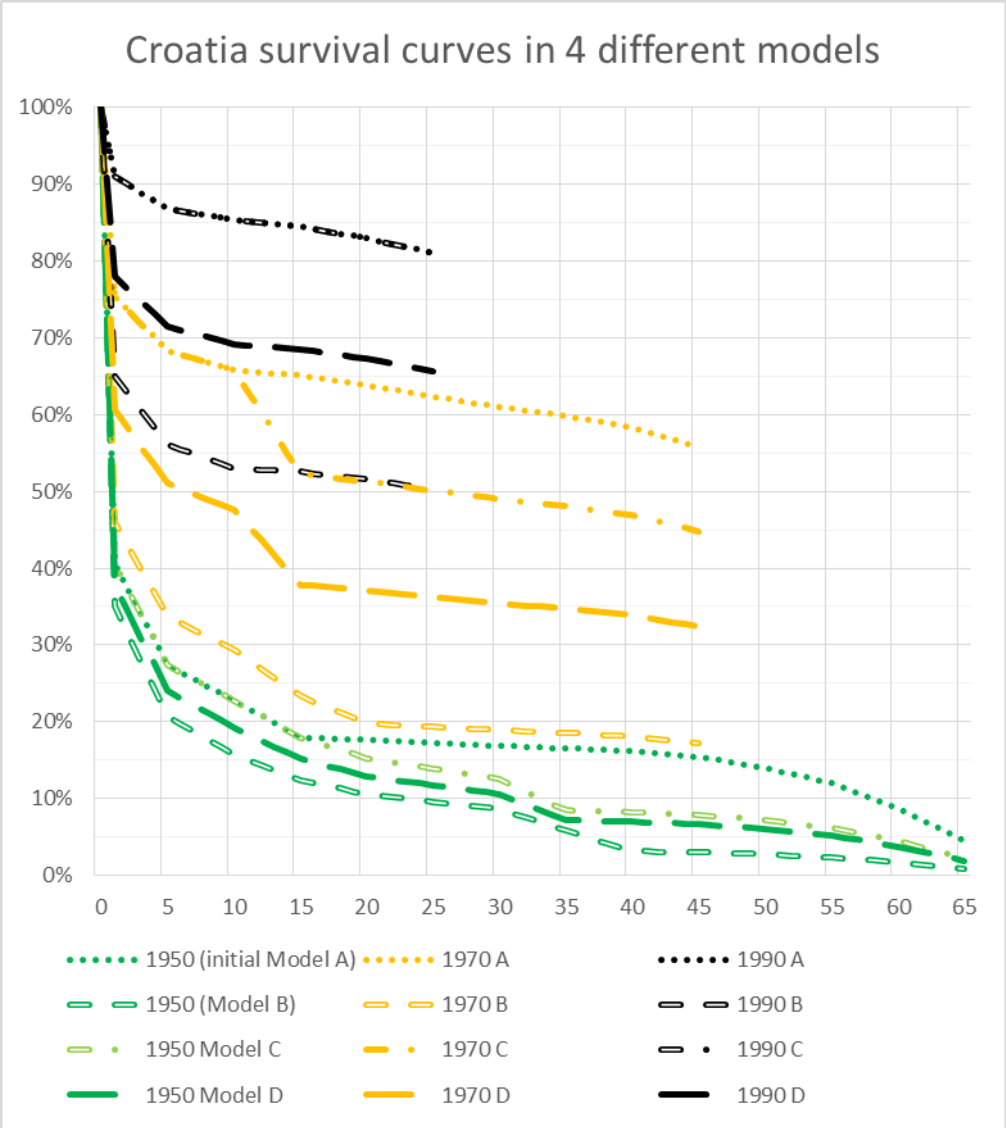
S5B. Constructing alternative survival models for former East bloc countries

In Supplementary Materials S4, we have explained how we constructed the initial model. The initial model matched the information on people with DS alive in the four former West bloc countries (with empirical data) (S5A). However, the initial model had a very poor fit for the four countries from the former East bloc. In S5C, we will see that this also applies to information on the age distribution of deaths of people with DS from national statistical offices. The initial model has a good fit to the empirical material on age at death in former West bloc countries, and a rather poor fit for former East bloc countries.

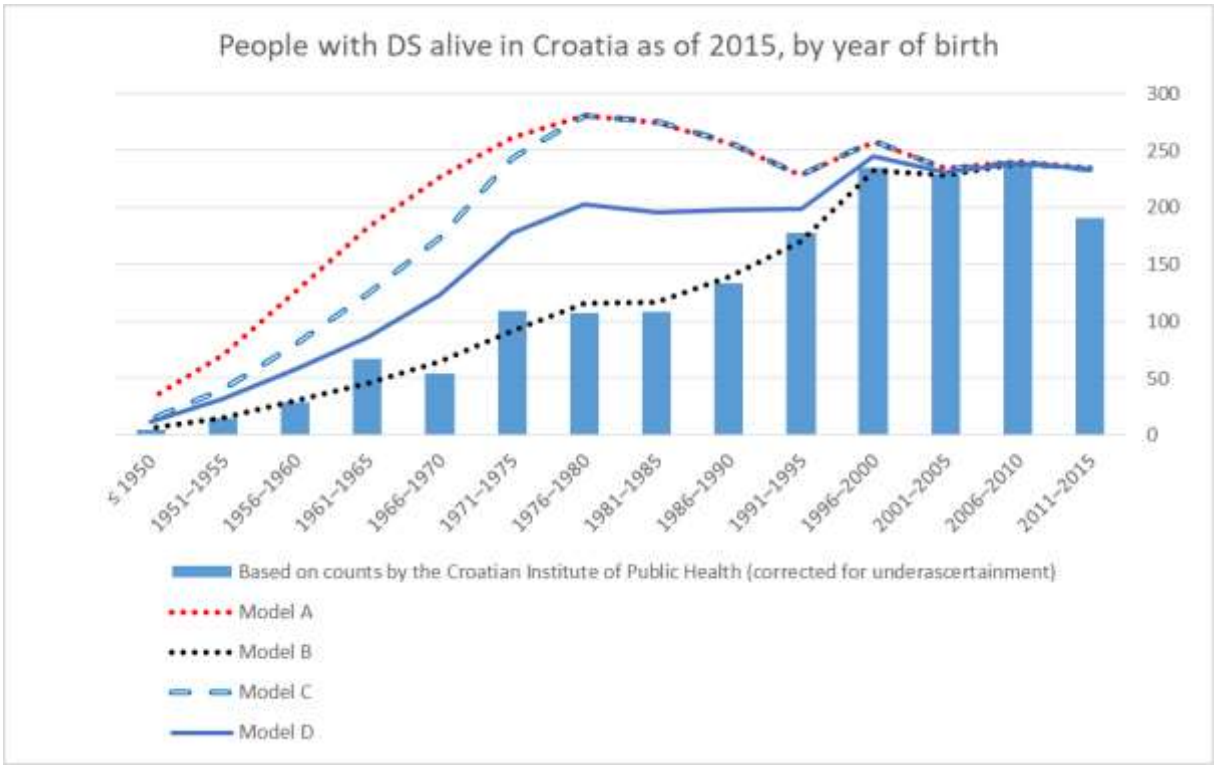
Therefore, we have developed an alternative model, which we will call "Model B." We have used the model that fit to the Croatian data on people alive (see S5A) as the mold because out of the four former East bloc countries, the model for Croatia seems to be the least extreme in lowering historical estimates of 1-year survival of people with DS. To take into account possible differences, in general, between countries' 1-year mortality—and supposedly a corresponding lower or higher quality of health care that will affect survival in DS, too—we applied the following procedure. If the value in the initial model for 1-year survival in people with DS for a certain 5-year period was 10% higher (or lower) than that from Croatia, we assigned a 10% higher (or lower) new value than that from Croatia according in the Model B, too. For instance, in the initial model, 1-year survival for 1965–1970 in Croatia was estimated at 68%; in Estonia, this was 77% (1.13 times higher). For Model B, this value was estimated to be 40% in Croatia and 1.13 times higher (45%) in Estonia. Following this procedure, Model B was developed for all of the East bloc countries with the exception of Albania, Romania, and Ukraine, for which we have used the models as developed in S5A.

Model B might be too extreme in lowering the historical estimates of 1-year survival in people with DS for the former East bloc. Secondly, one of the effects of lowering the 1-year survival estimates (and the corresponding 5- and 10-year survival rates) is that when the 1-year survival is estimated to be less than 60%, the survival rates above 10 years of age are also adapted to a much more hazardous survival curve (based on counts by Penrose in 1949 (see S4). In Model B, the more hazardous survival curve above 10 years of age was, in effect, up to 1990. Subsequently, we wondered whether only adapting the survival rates above 10 years of age (and not lowering the 1-, 5, and 10-year survival rates) would have a similar effect on the modeled age distribution of deaths of persons with DS (Model B)—or, perhaps, would even have a better fit. We tried this assumption on Croatia and Estonia. Lowering only the survival rates above 10 years of age up to 1990 did not have the correct effect, as that led to an age distribution of deaths for people with DS between 2005–2015 with too low of numbers of deaths above 55 years of age and too high of numbers between 10–25 years of age. However, lowering the survival rates above 10 years of age up to 1980 led to an age distribution that was much more similar to the empirical data. We have defined this as "Model C."

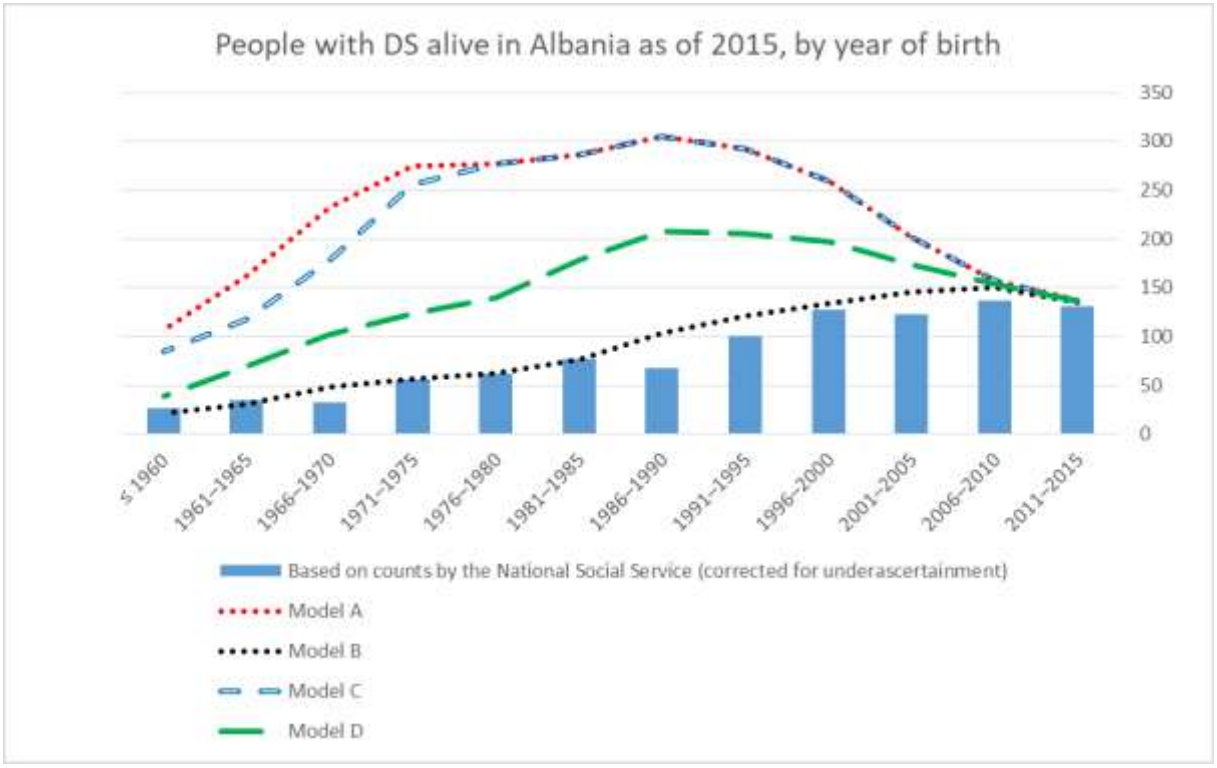
However, the assumption that only survival above 10 years of age would historically be less favorable in former East bloc countries seems not to be fully logical. As a final exploration, we developed "Model D," in which survival above 10 years of age up to 1980 is less favorable (as it is in Model C), but 1-year survival is adapted to a value that is the mean of the value of model A (which is the same value as in Model C) and Model B. So estimates of 1-year survival (and corresponding 5- and 10-year survival) for people with DS before 2000 are lowered in comparison to model A, but less extreme than in Model B. In the graph below, the survival curves for the year of birth 1950, 1970, and 1990, in the four different models are shown for Croatia. (For 1990, Model A is equal to Model C.)

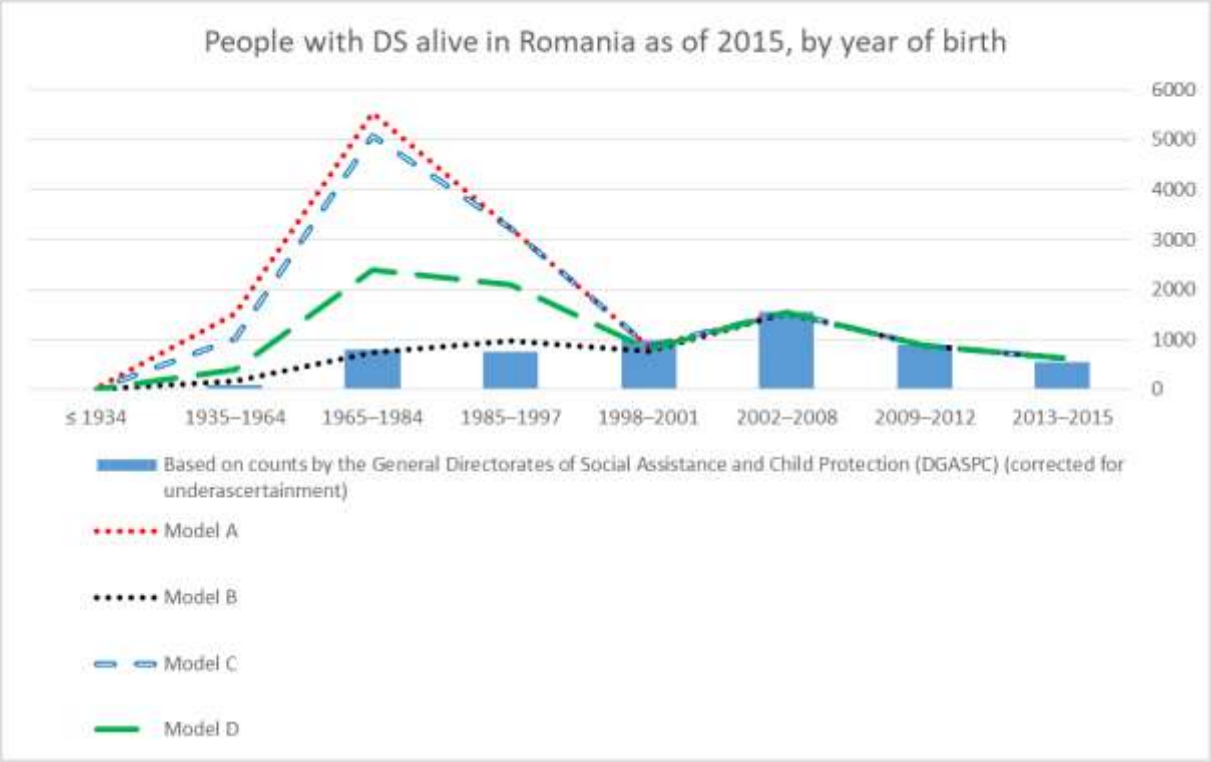


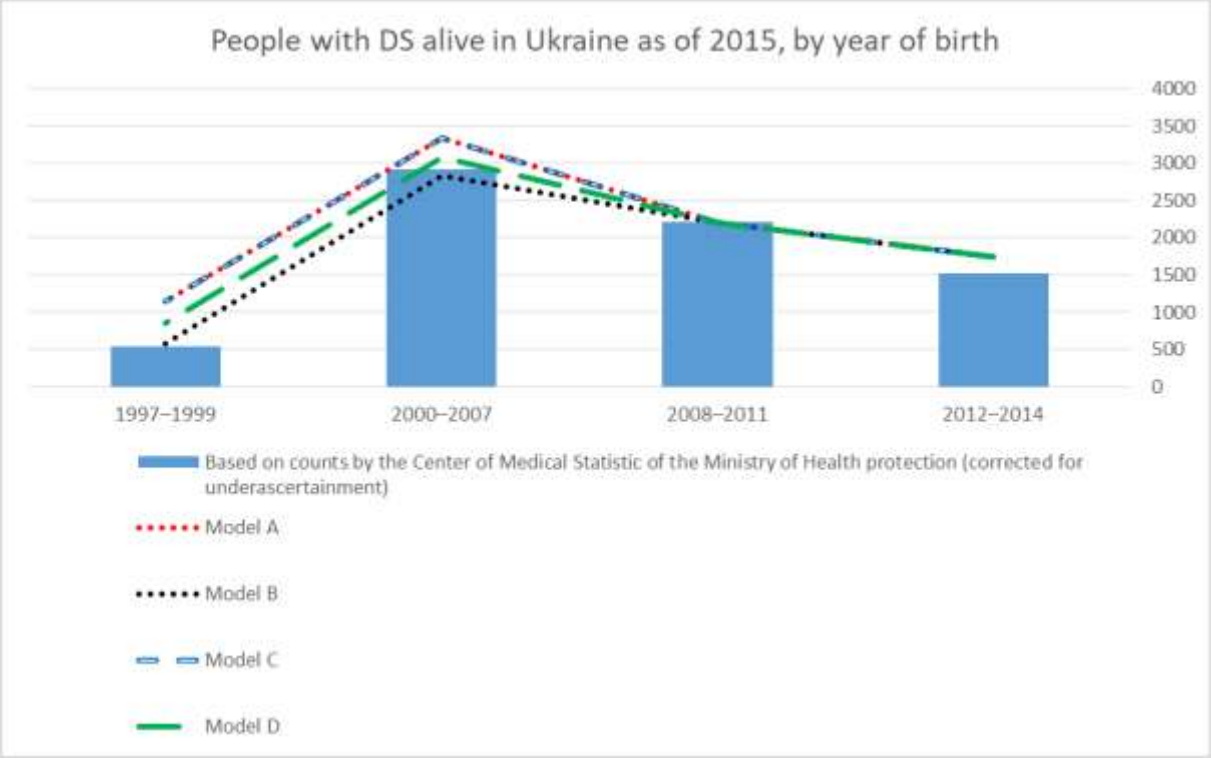
As we have seen in S5A, Model B was constructed in such a way that it fits the data of people alive in Croatia (corrected for under-ascertainment). In the graph below, the estimates as of 2015 based on counts by the Croatian Institute of Public Health (corrected for under-ascertainment), by year of birth, are compared with the other models, as well. If Model B is incorrect, this would imply huge under-ascertainment in the data of the Croatian Institute of Public Health for the birth cohorts born before 1990 (i.e., older than 25 years of age in 2015).



For Albania, Romania, and Ukraine, respectively, the corresponding graphs are below.







Subsequently, in Supplementary Materials S5C, we have applied Model A to the former West bloc countries, and the four different models to the former East bloc countries, to explore the similarity of the modeled age distribution of deaths for people with DS with this age distribution in national death statistics.

S5C. Comparison of age at death[1] of people with DS

The WHO Mortality DataBase (MDB) comprises deaths registered in national vital registration systems, with underlying cause of death coded by the relevant national authority. The raw data can be downloaded at https://www.who.int/healthinfo/statistics/mortality_rawdata/en/ (accessed September 17, 2019). These data are official national statistics transmitted to the World Health Organization. However, the WHO warns that these national systems can be incomplete.

In the data files that are based on ICD-10 codes (not all countries used ICD-10; and only the countries that used ICD-10 have DS as a separate code), information on the number of deceased people with DS as primary cause of death, by age at death, and year of death can be found for many different countries, covering the period 1994–2017, or often a shorter series of years within this period. As national systems can be incomplete, and as deceased people with DS will not always be registered as having died with DS as the primary cause of death, these data cannot be interpreted as covering every deceased person with DS in a country. However, assuming the resulting "under-registration" is not dependent on the age of the person, we could treat these data as a depiction of the age distribution of deaths of people with DS and compare this information with predictions of the distribution of the age at death that our model can produce for different calendar years.

We have made the comparison in three different ways:

1. We have summed all data on deaths of people with DS for 2005–2015 (or for a shorter period inside this interval, if data were not available for all years), separately for the WHO data and for the modeled data, and we have estimated the distribution of deaths over age groups.

2. We have summed all data on deaths of people with DS for 1994–2004, (or if 1994 was not available, 1995–2005, etc.), separately for the WHO-data and for the modeled data, and have estimated the distribution of deaths over age groups.

3. We have estimated the 25th percentile, 50th percentile, and 75th percentile of these ages of death by year. The WHO reports the data up to 5 years of age by single year, and above, by 5-year group. For the value 5–9, we assigned the value 7, etc. To minimize random fluctuation by year, in analyzing the WHO data, we made 5-year running averages. For the first and last data point in each time series, we used 3-year averages (for instance, if data were available up to 2016, the 50th percentile for 2015 actually is the average of the 50th percentile for 2014, 2015, and 2016).

However, in regards to our assumption that "under-registration" is independent of age, we actually suspected that if children with DS died in the first year of life, the chance to be reported with DS as primary cause of death would probably be higher because a doctor would be more inclined to report

[1] "Age at death" should not be confused with "life expectancy." **Age at death** refers to the age distribution of people who died in a specific calendar year, which is strongly influenced by the age distribution of the live population. **Life expectancy** is the number of years children born in a specific year of birth are expected to live. These constructs are different. For example, modeled *mean* **life expectancy** for DS in Europe as of 2015 varies between 48 (for Albania) to 53 (for Scandinavian countries) years of age, and it is not different for the different Models (A, B, C, and D). Corresponding *median* **life expectancy** is between 57 (Albania) and 59 (Scandinavian countries) years of age. In contrast, modeled *mean* **age at death**, as of 2015, using Model D for former East bloc countries, varies more widely, i.e. between 31 years of age (for Albania) to 55 years of age (for Finland). Corresponding *median* **ages at death** are, respectively, 36 and 59 years of age. In addition, age of death is different for the different Models. For instance, for Albania, as of 2015, it varies between Model A's prediction of mean age at death of 40, and Model B's projection of 25 years of age. Corresponding median ages of death are 47 and 21 years of age, respectively.

DS as primary cause of death when a person is an infant, than when they are older. For Germany between 1980–2015 (see S1C), we estimated that around 85% of deaths of children with DS, under 1 year of age (as modeled), were registered in the counts by the German statistical office. For the Netherlands, the corresponding percentage (for 1996–2015) was 89%. Below, when we account for all deaths taken together, Germany reported on 42% of the modeled numbers, and the Netherlands on 45%, which suggests a difference in assigning DS as primary cause of death in young children compared to older age groups. In the analysis below, we made use of the raw data without a correction for this effect. As a result, the percentage of children less than 1 year of age in the empirical data on deaths might actually be over-estimated. In many of the countries, also in countries with a very good fit between WHO-MDB data and modeled data, the model produces a bit lower estimate of the percentage at deaths in the age group 0–4 years.

Countries from the former West bloc

Below, we will present the data from the former West bloc countries. For 3 of these countries, numbers of deceased people with DS in the WHO Mortality Database (MDB) are so low that it would not be purposeful to make a comparison with the model. For the other 16 countries, a comparison was possible. For most countries, it was possible to compare two rows of years (e.g., 2005–2015 and a period starting with the first available year in the MDB like 1995–2005). With the exception of Greece, which we believe is a result of randomness in the data and for which data were available for only 3 years (2014–2016), the MDB data and the model had a very good fit with a Pearson correlation for each country at least 0.9 between the age distribution in MDB and our model.

On average, 77% (range 63–90%) of the deceased individuals with DS in the MDB are 45–70 years of age in these former West bloc countries for the period 2005–2015. Our model predicted an average of 74% (range 66–79%). Pearson correlation between MDB percentages by country and model is 0.6 ($p < 0.014$) (a high correlation implies that a higher percentage of people with DS in the age range 45–70 in the MBD is accompanied by a higher percentage in this same age range in the predictions). If we look at the older range of years (1994–2004 or, if 1994 is not available, then 1995–2005, etc.), the MDB has 72% (range 57–80%) in the age range 45–70, and our model predicted 69% (range 63–73%). For these older range of years, Pearson correlation between MDB and model was 0.75 ($p = 0.003$).

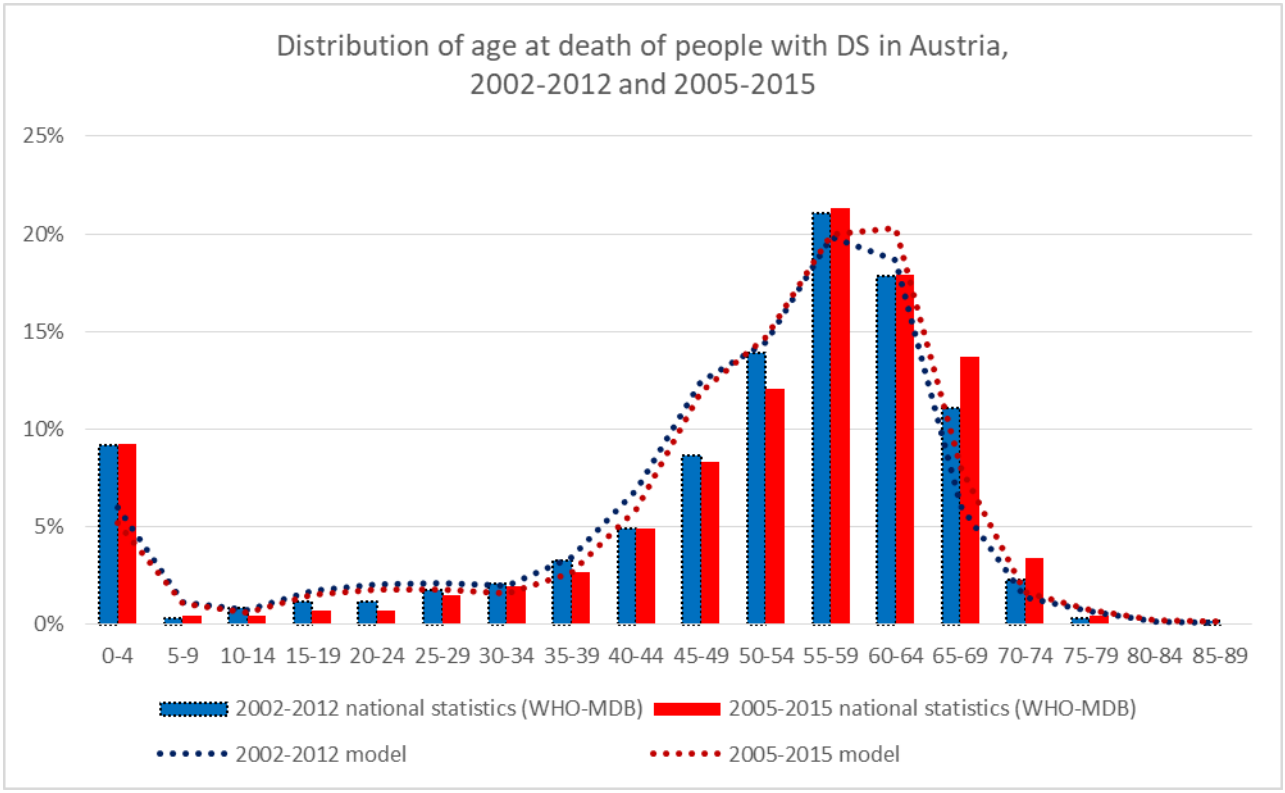
For Denmark, Finland, and Spain, the comparisons of people by age at death do not show that the model overestimates numbers in the older age groups. The percentages in the MDB and those according to the model are very similar. This corroborates our conclusion that the discrepancy between model and counts in the older age groups of people alive (see S5A) in Denmark, Finland, and Spain are a result of under-ascertainment in the counts of people alive, and not of the model overestimating survival in these older birth cohorts.

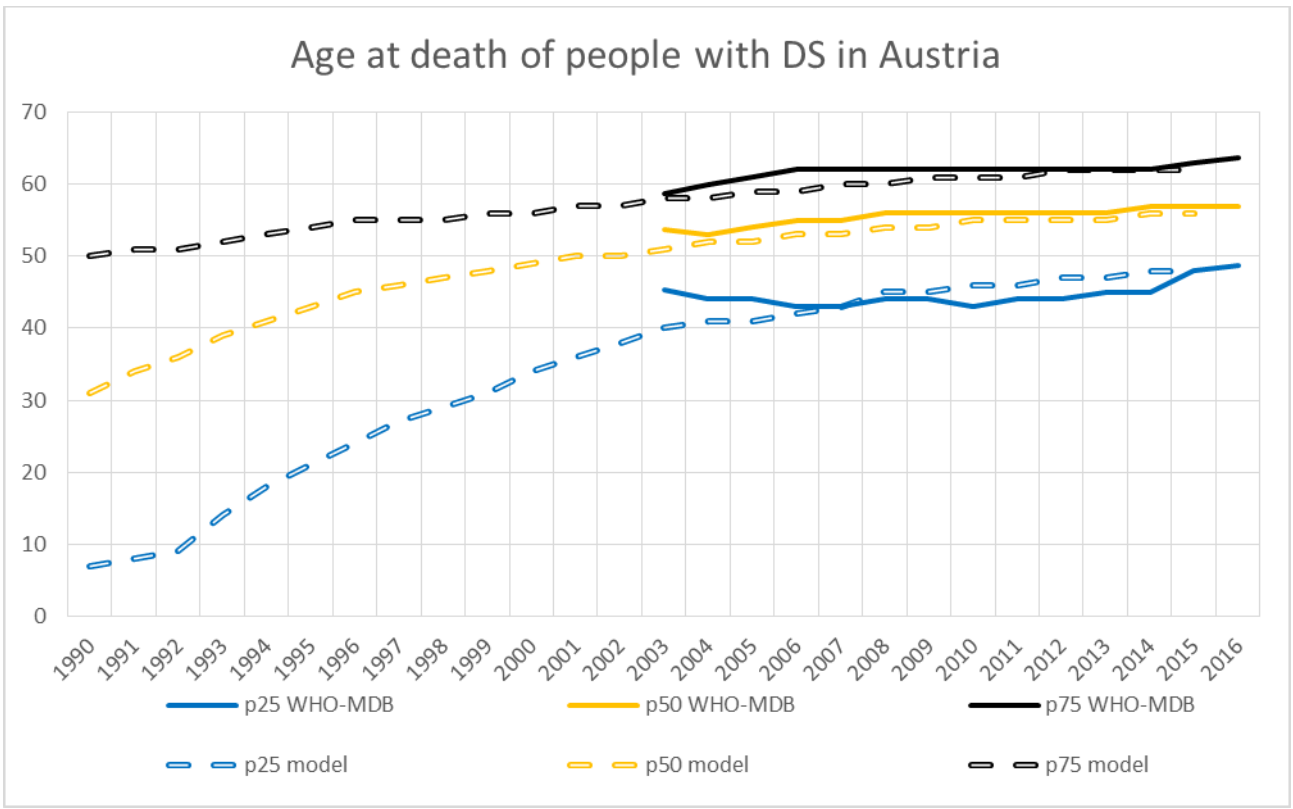
Finally, we will analyze the data from all former West bloc countries pooled.

Western Europe

Austria

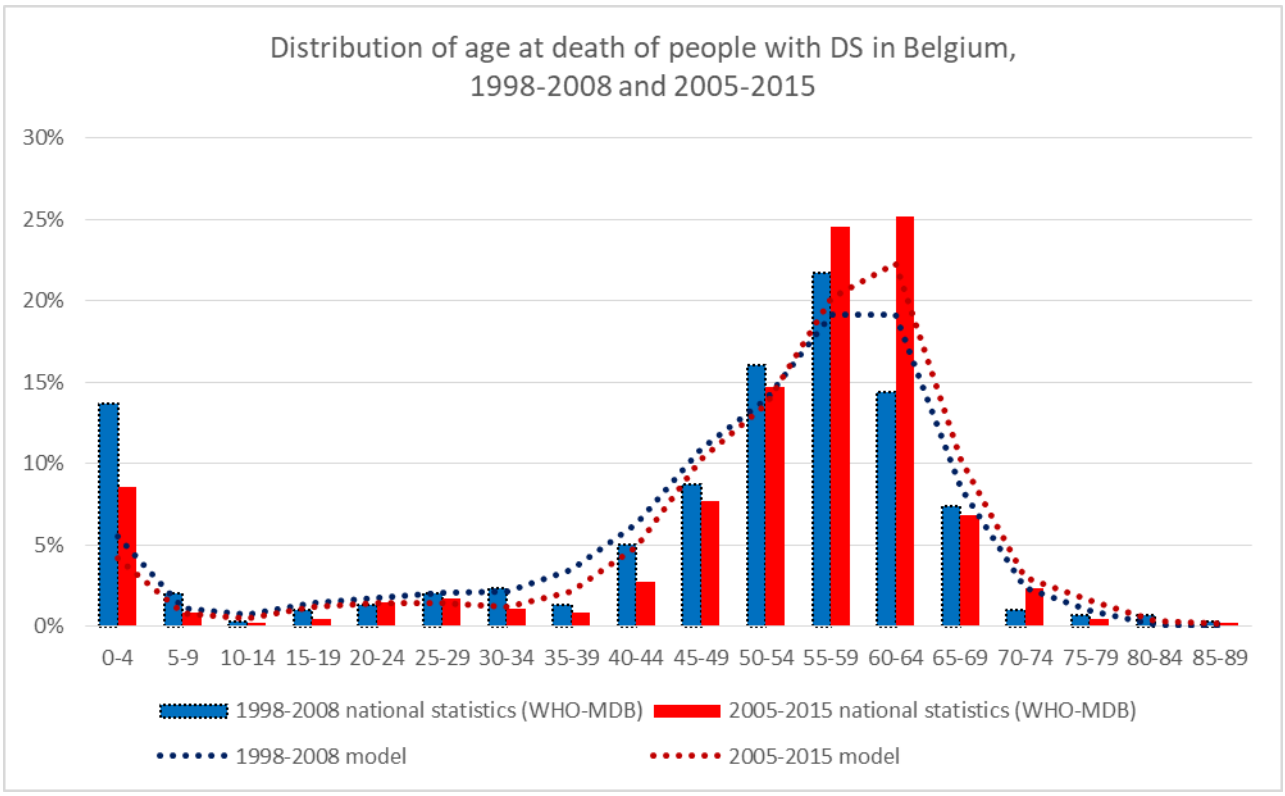
The WHO Mortality Database (MDB) reports data on DS as cause of death for Austria for the period 2002–2017. For 2005–2015, data are available on 670 deceased people with DS, which is 69% of what our model projects. For 2002–2012, there are 612 deceased people and 70% projection. For 2005–2015, correlation between MDB and our model (graph below) is 0.95 ($p < 0.000$); for 2002–2012, it is 0.96 ($p < 0.000$).

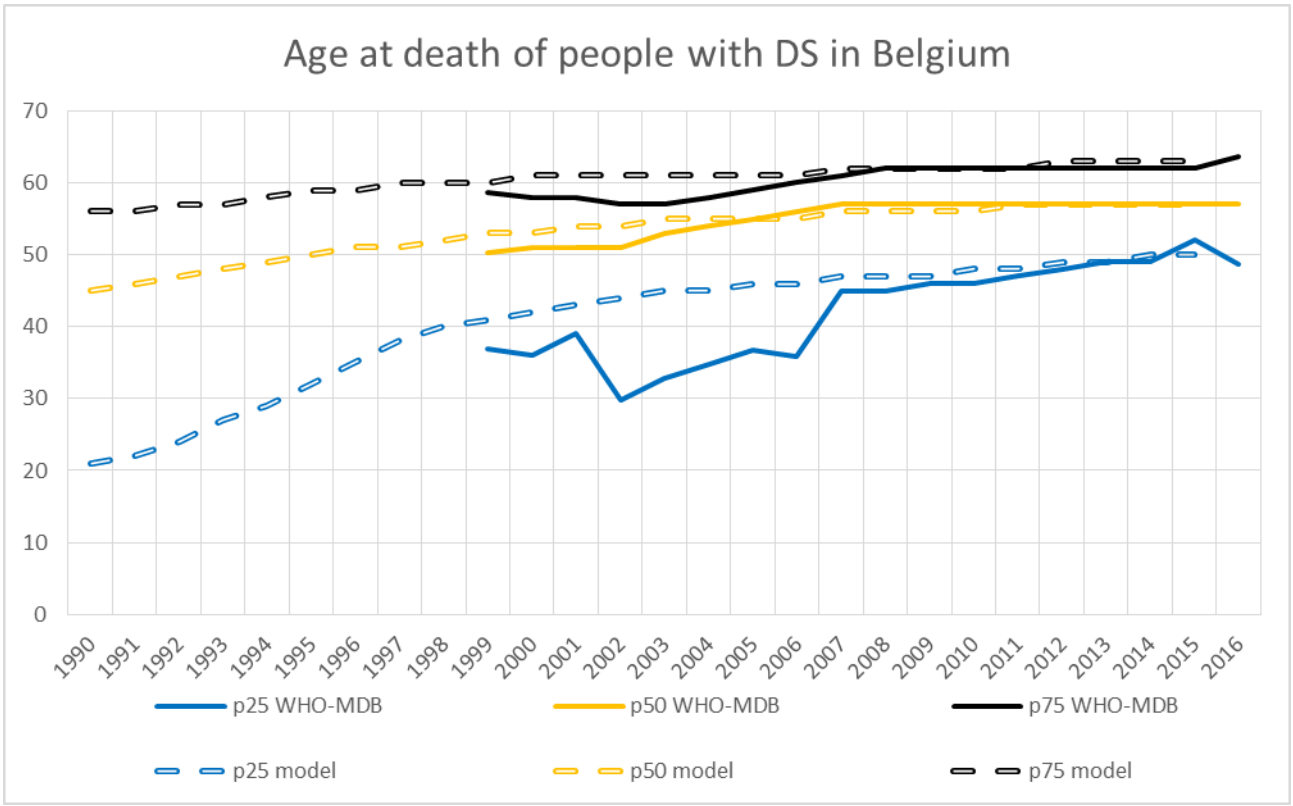

Distribution of age at death of people with DS in Austria,
2002-2012 and 2005-2015
25%
20%
15%
10%
5%
0%
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
2002-2012 national statistics (WHO-MDB)
2005-2015 national statistics (WHO-MDB)
2002-2012 model
2005-2015 model


Age at death of people with DS in Austria
70
60
50
40
30
20
10
0
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model
p50 model
p75 model

Belgium

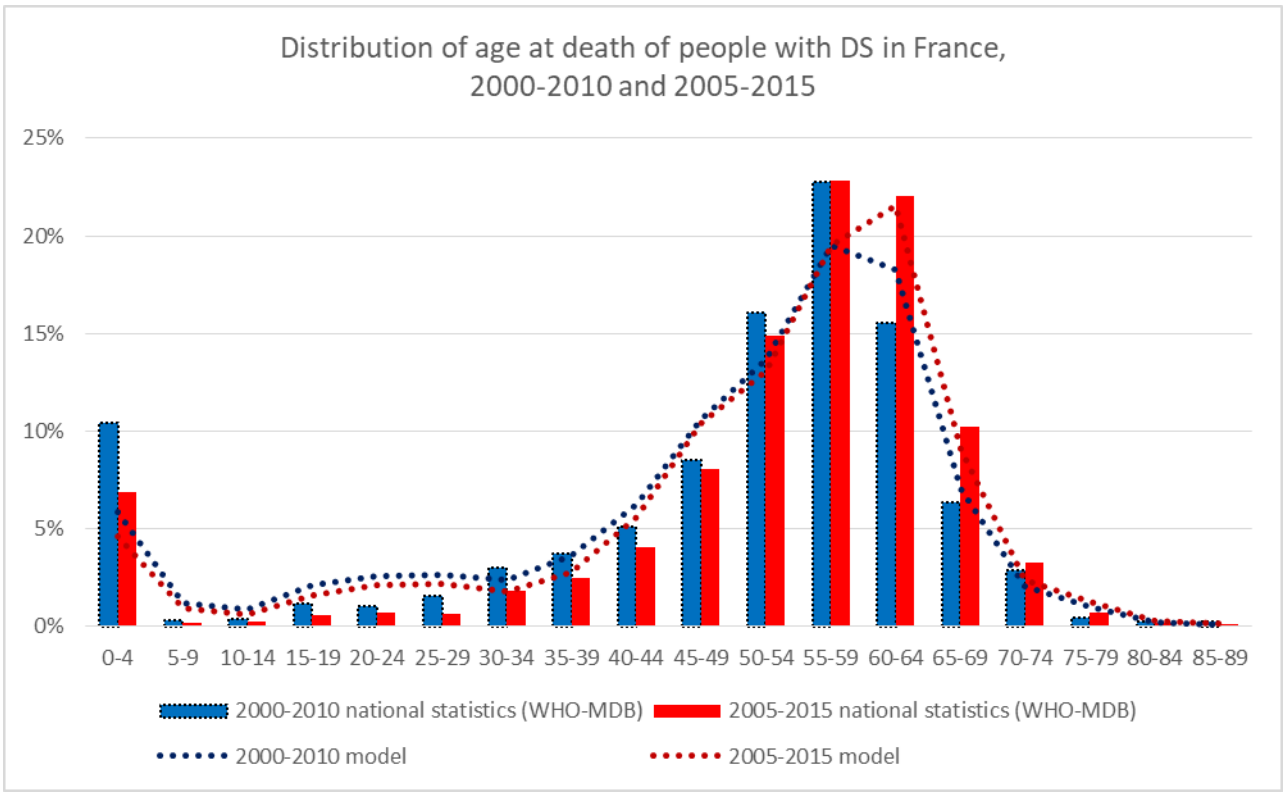
The WHO Mortality Database reports data on DS as cause of death for Belgium for the period 1998–2017. The MDB contains data on 468 people with DS that died between 2005–2015, which is 34% of the number projected by the model for the same period. For 1998–2008, it is 299 and 26%, respectively. For 2005–2015, correlation between MDB and model is 0.97 ($p < 0.000$); for 1998–2008, it was 0.92 ($p < 0.000$).

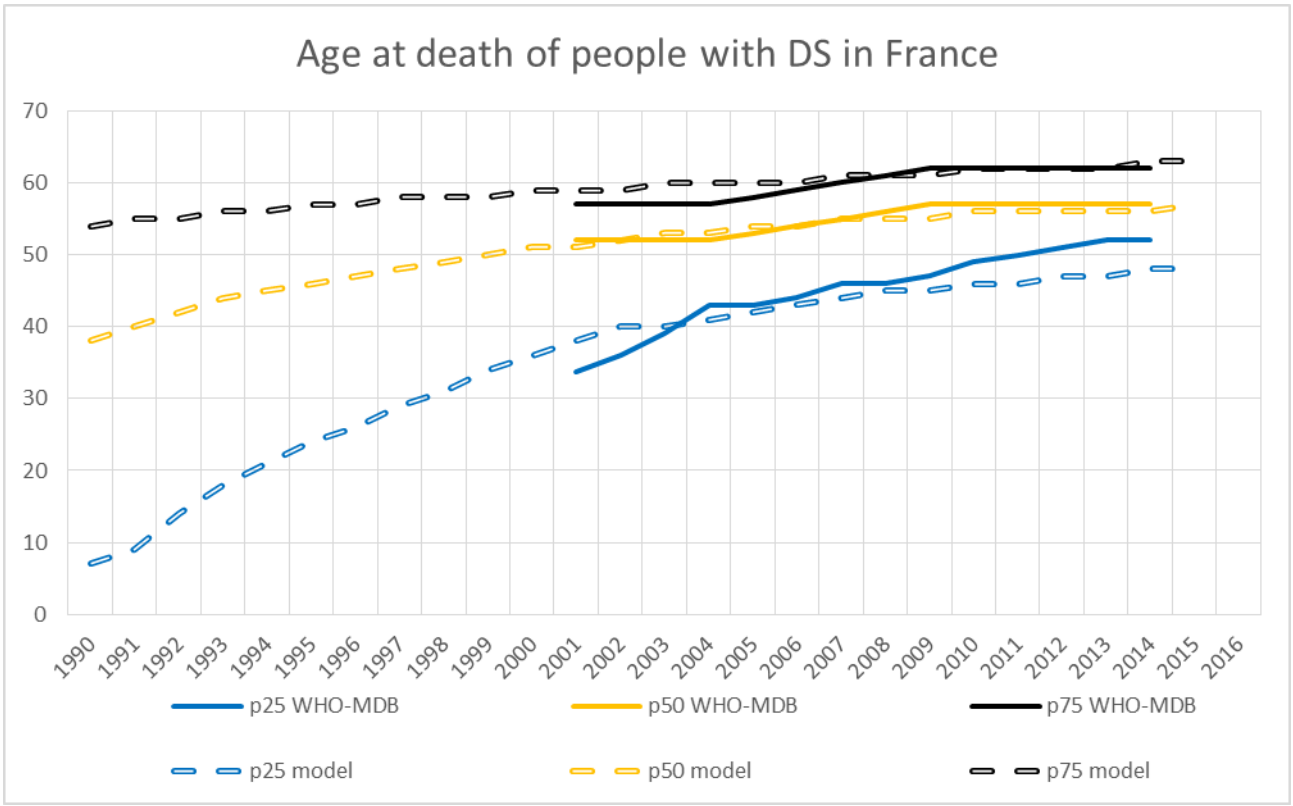




France

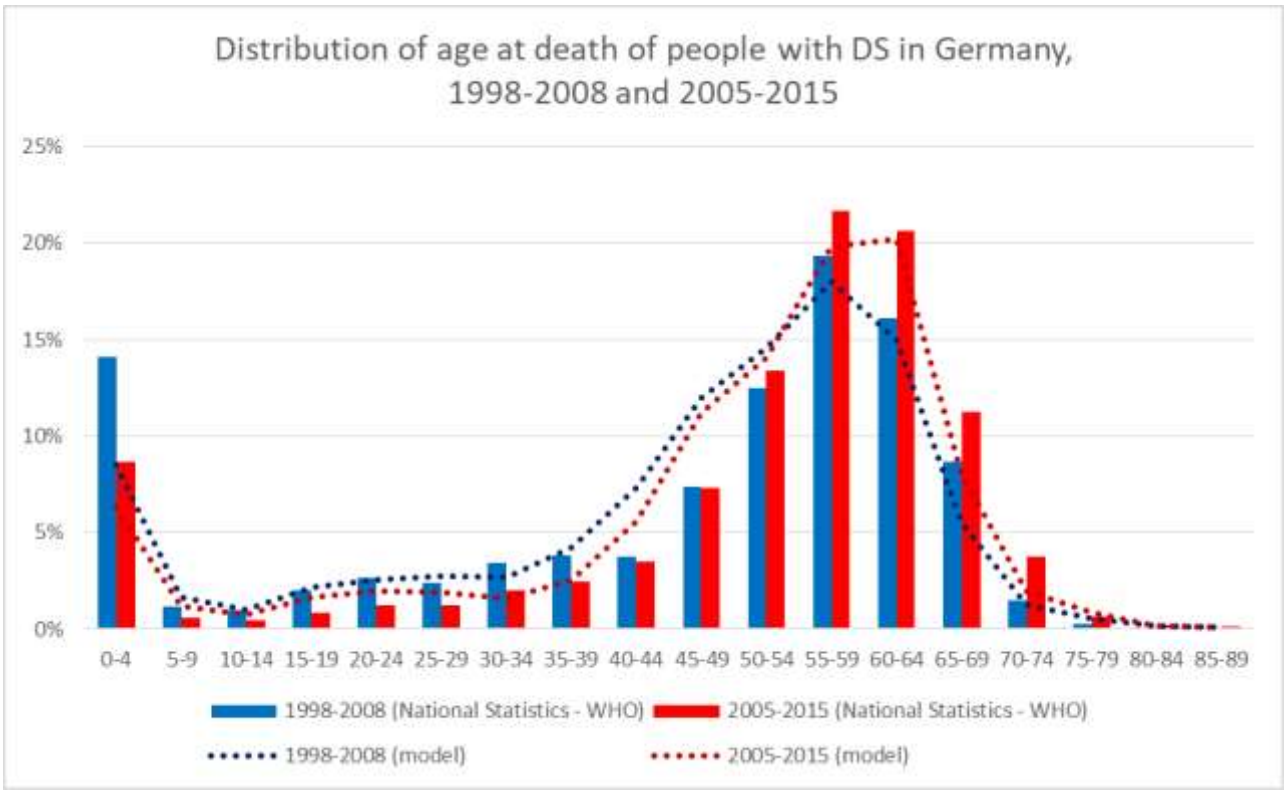
The WHO Mortality Database reports data on DS as cause of death for France for the period 2000–2015. The MDB contains data on 2,711 people with DS that passed between 2005–2015, which is 37% of the number projected by the model for the same period. Corresponding data for 2000–2010 are 2,141 and 34%, respectively. For 2005–2015, correlation between MDB and model is 0.98 ($p < 0.000$); for 2000–2010, it is 0.96 ($p < 0.000$).

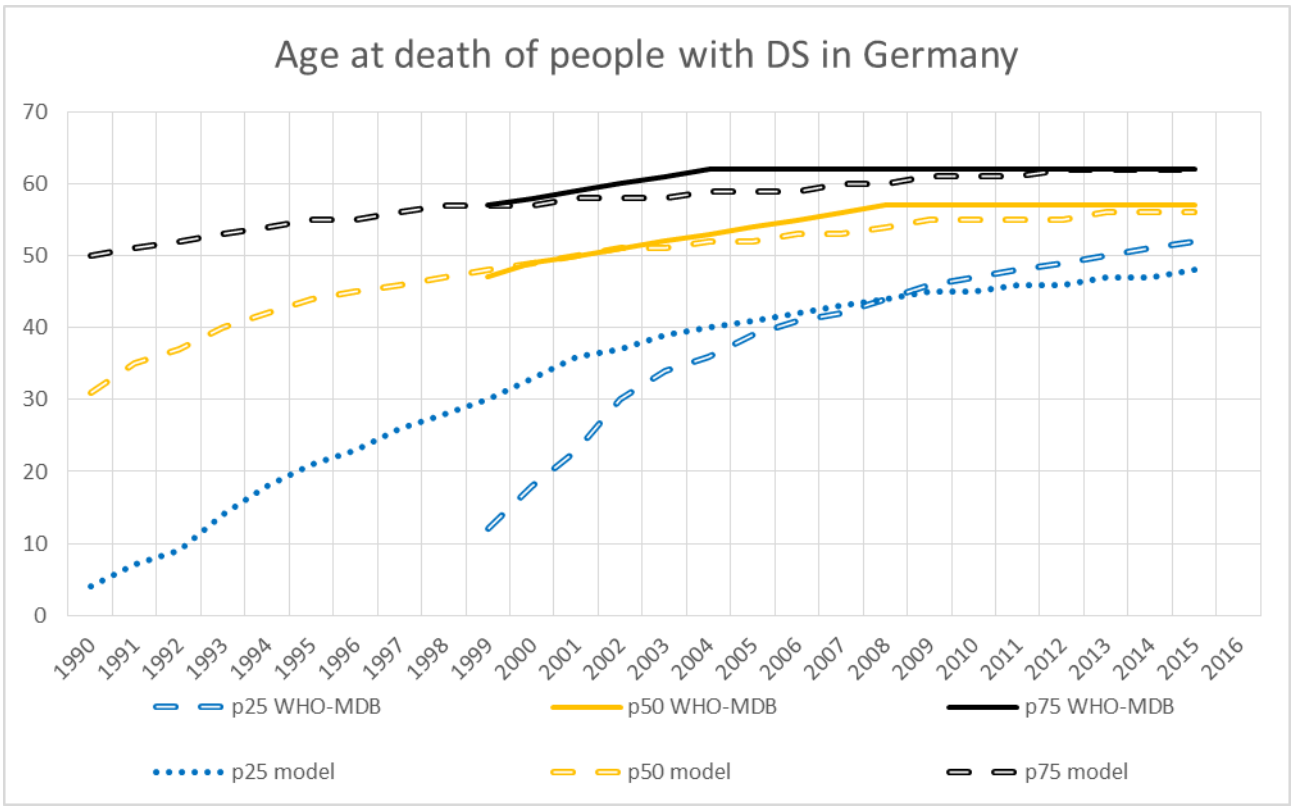




Germany

The WHO Mortality Database reports data on DS as cause of death for Germany for the period 1998–2016. The MDB contains data on 3,971 people with DS that died between 2005–2015, which is 42% of the number projected by the model for the same period. For 1998–2008, it is 2,727 and 38%, respectively. For 2005–2015, correlation between MDB and model is 0.97 ($p < 0.000$); for 1998–2008, it was 0.93 ($p < 0.000$).



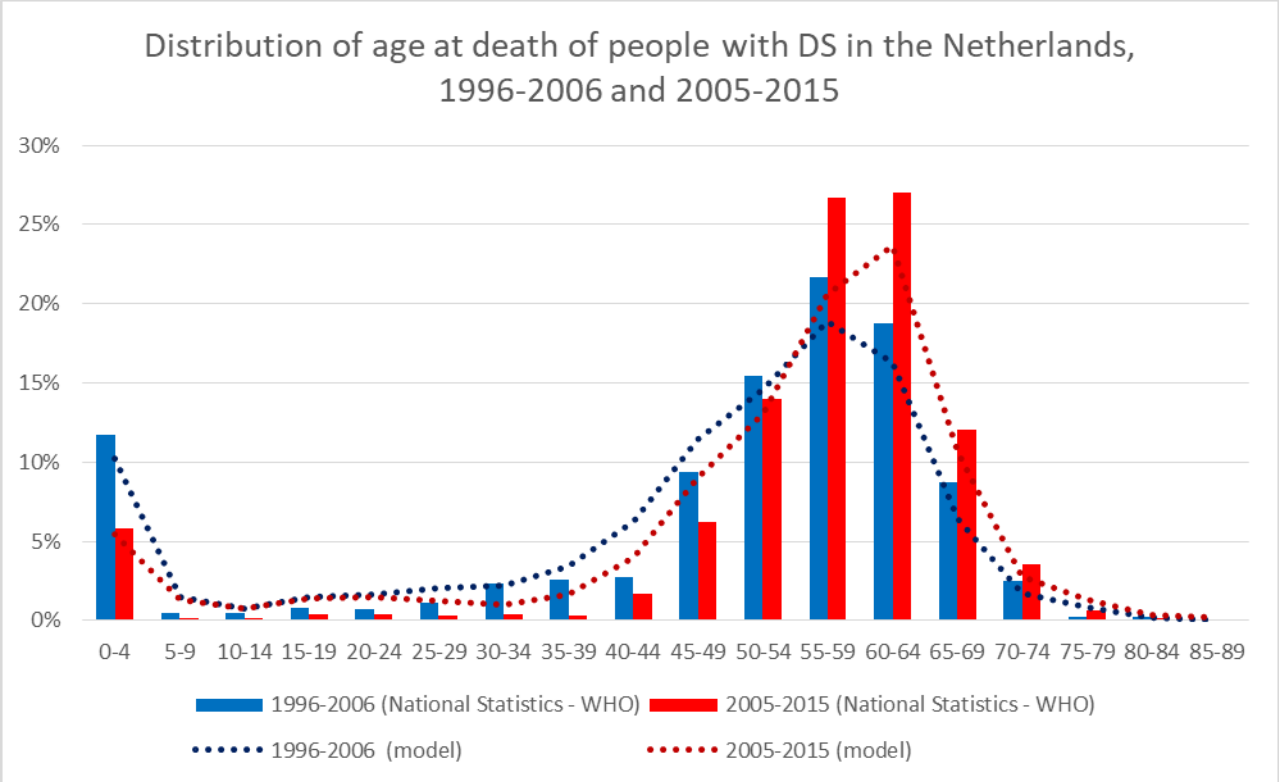


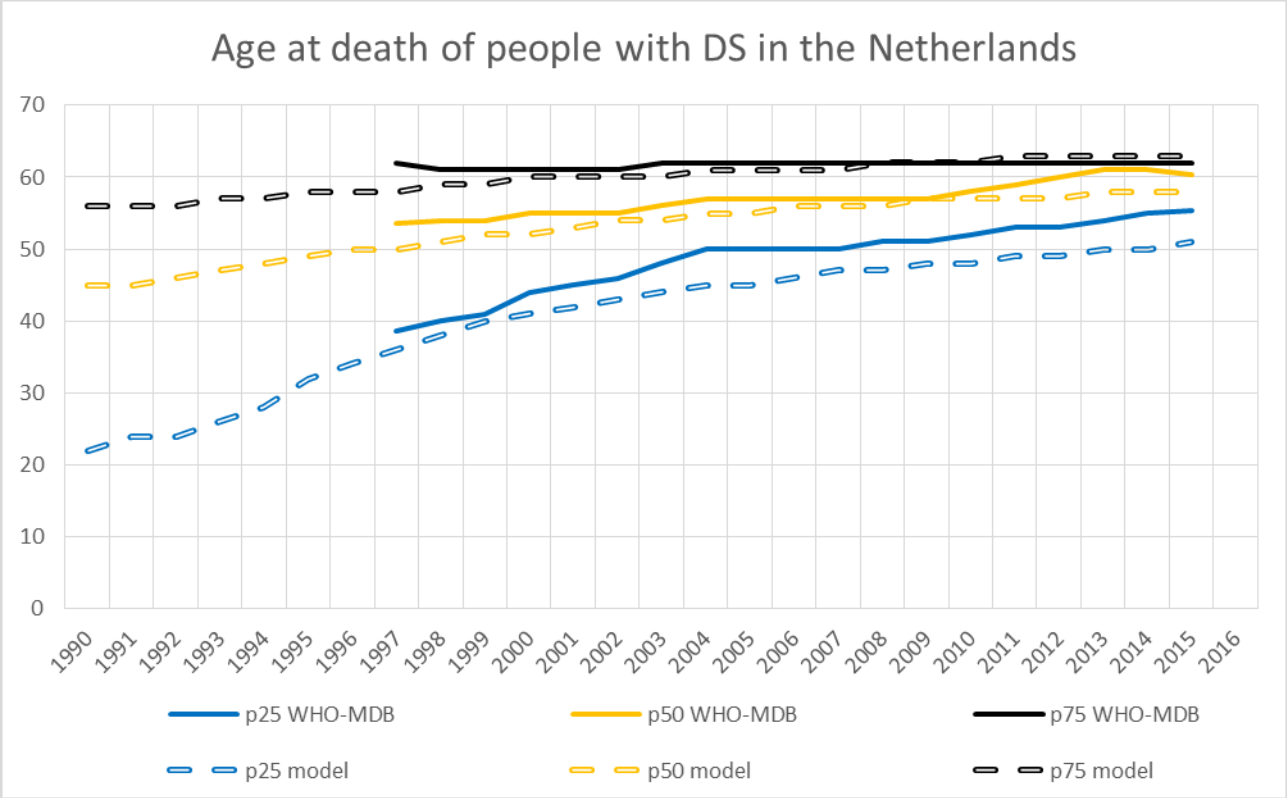
Luxembourg

The WHO Mortality Database reports data on DS as cause of death for Luxembourg for the years 2010 and 2012–2016. In total 11 deaths are reported, 52% of what the model predicts for the same years. However, numbers in the MBD are so low that looking at the age distribution would not be purposeful.

Netherlands

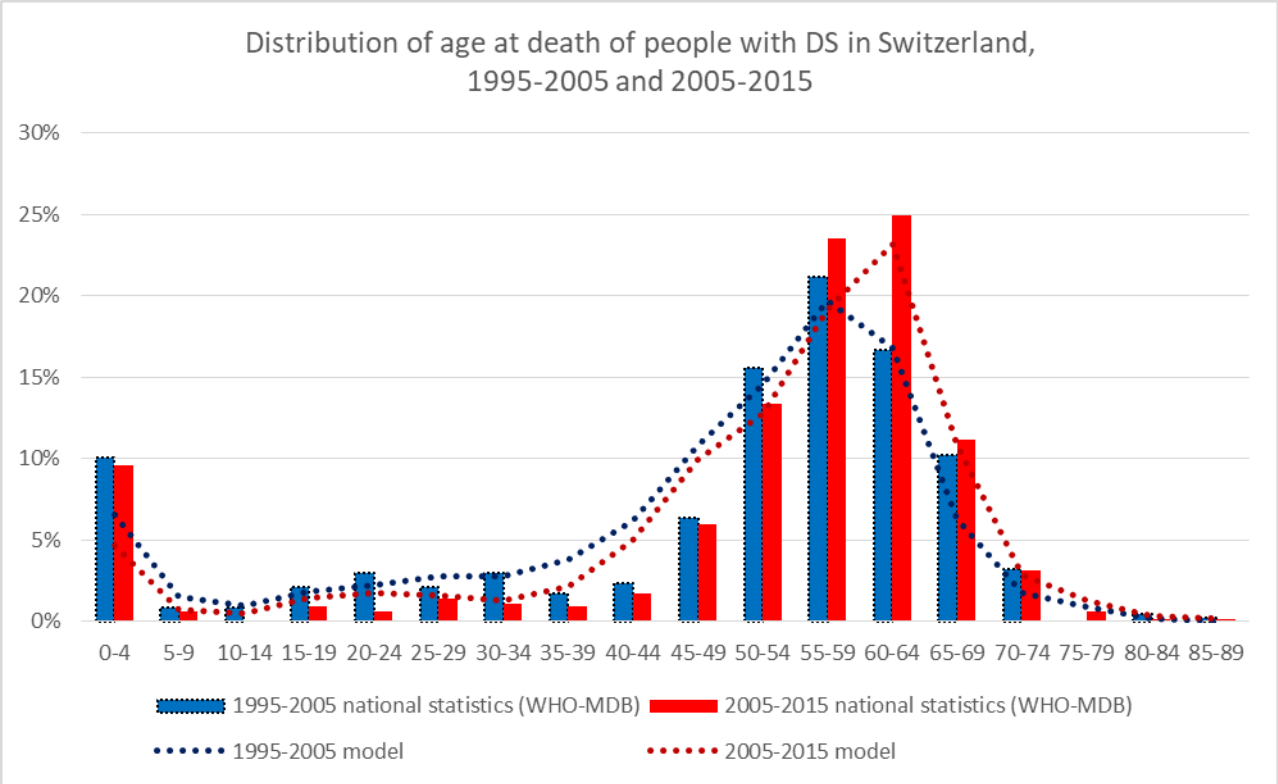
The WHO Mortality Database reports data on DS as cause of death for the Netherlands for the period 1996–2016. The MDB contains data on 1,439 people with DS that passed between 2005–2015, which is 45% of the number projected by the model for the same period. For 1996–2006, it is 1,123 and 46%, respectively. For 2005–2015, correlation between MDB and model is 0.99 ($p < 0.000$); for 1996–2006, it was 0.98 ($p < 0.000$).

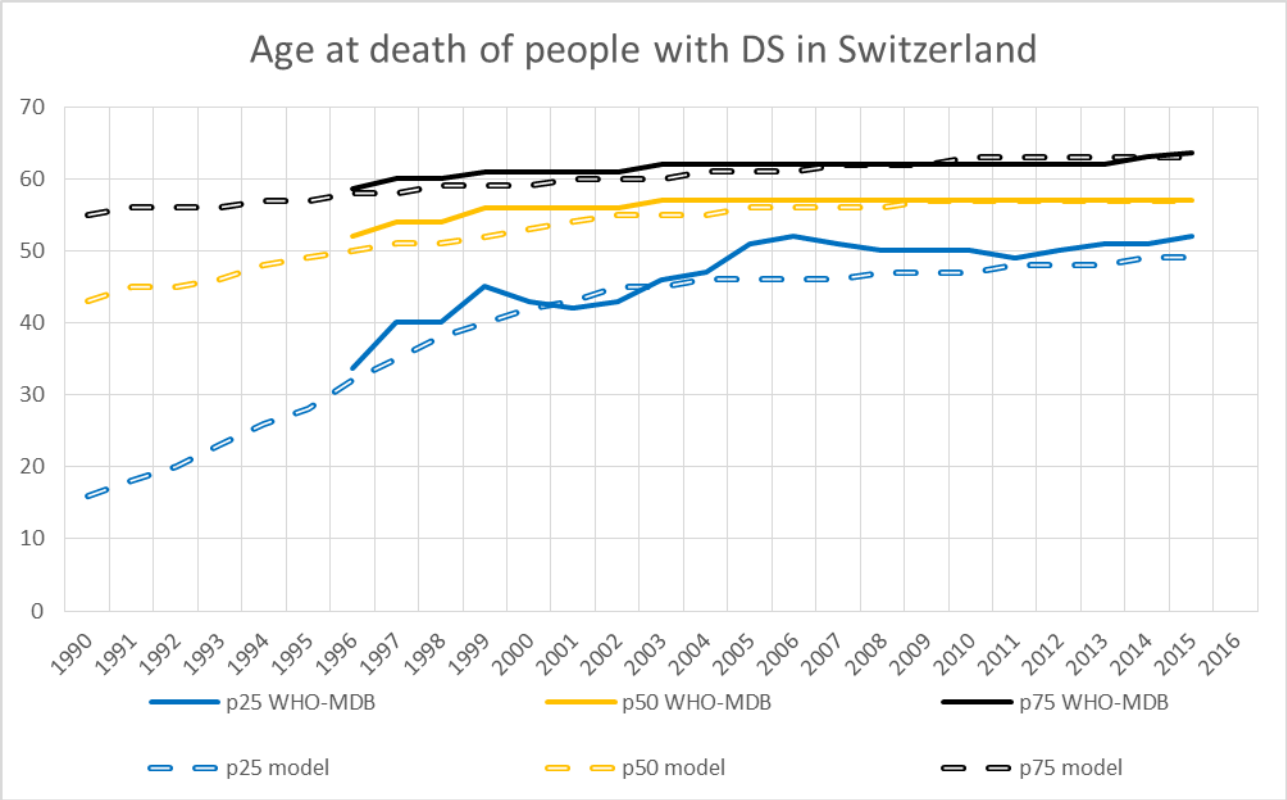




Switzerland

The WHO Mortality Database has data available for 1995–2016. The MDB contains data on 637 people with DS who died between 2005–2015, which is 64% of the number projected by the model for the same period. For 1995–2005, it is 468 and 62%, respectively**.** For 2005–2015, correlation between MDB and model is 0.97 ($p < 0.000$); for 1995–2005, it is 0.95 ($p < 0.000$).

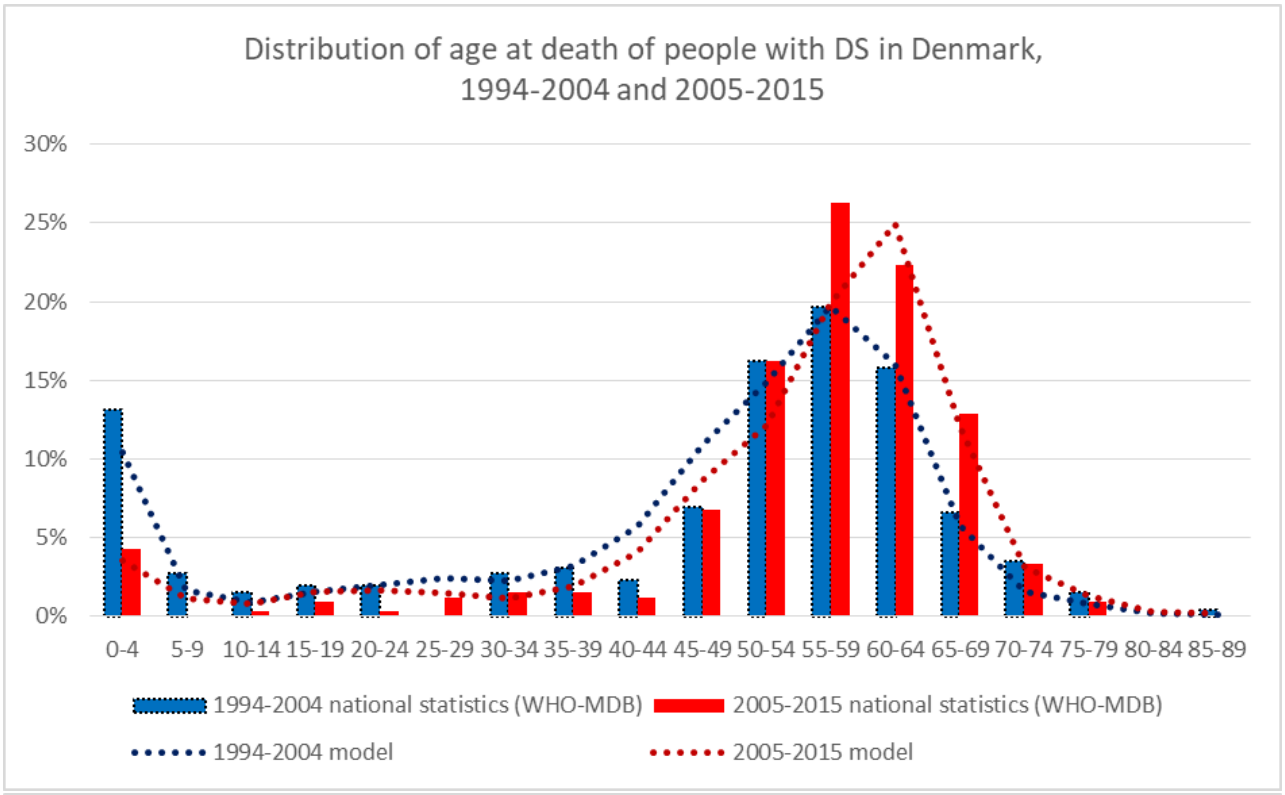


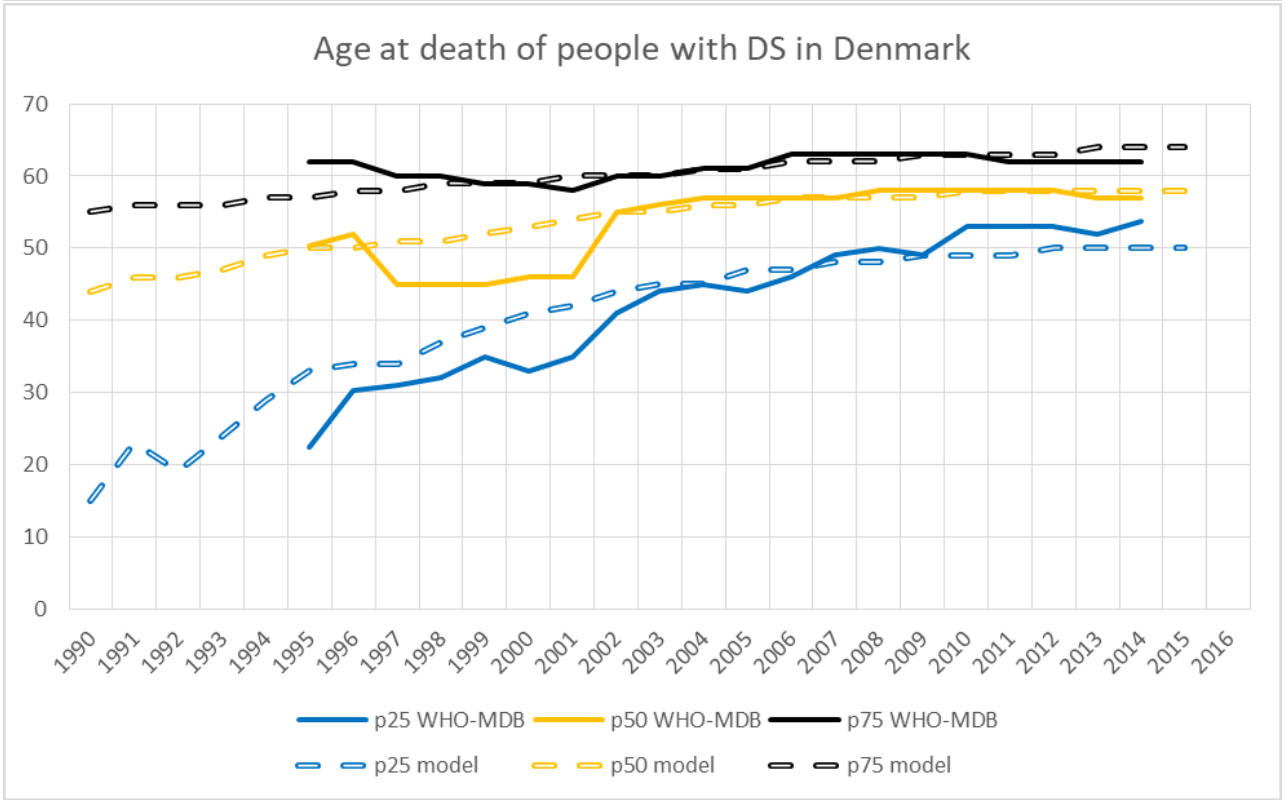


Northern Europe

Denmark

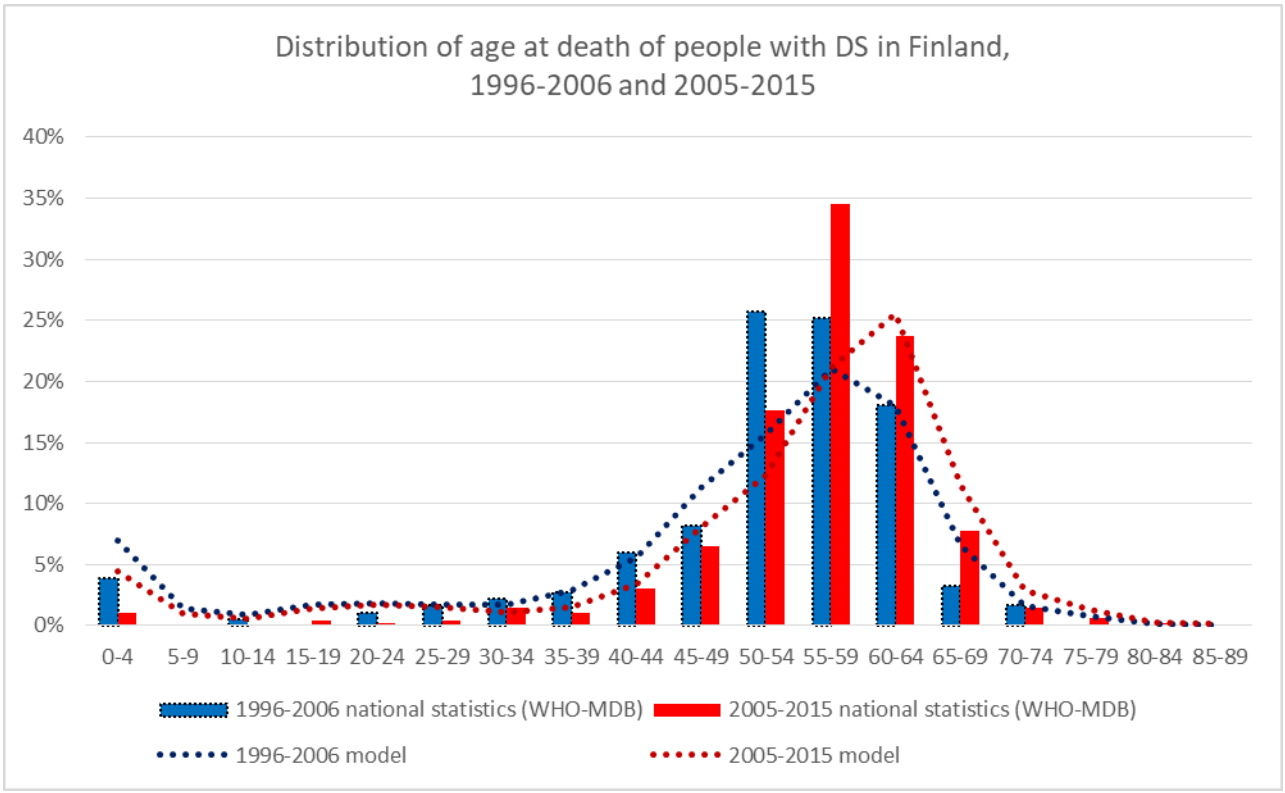
The WHO Mortality Database has data available for 1994–2015. The MDB contains data on 327 people with DS who died between 2005–2015, which is 46% of the number projected by the model for the same period. For 1994–2004, it is 259 and 46%, respectively**.** For 2005–2015, correlation between MDB and model is 0.97 ($p < 0.000$); for 1994–2004, it was 0.96 ($p < 0.000$).

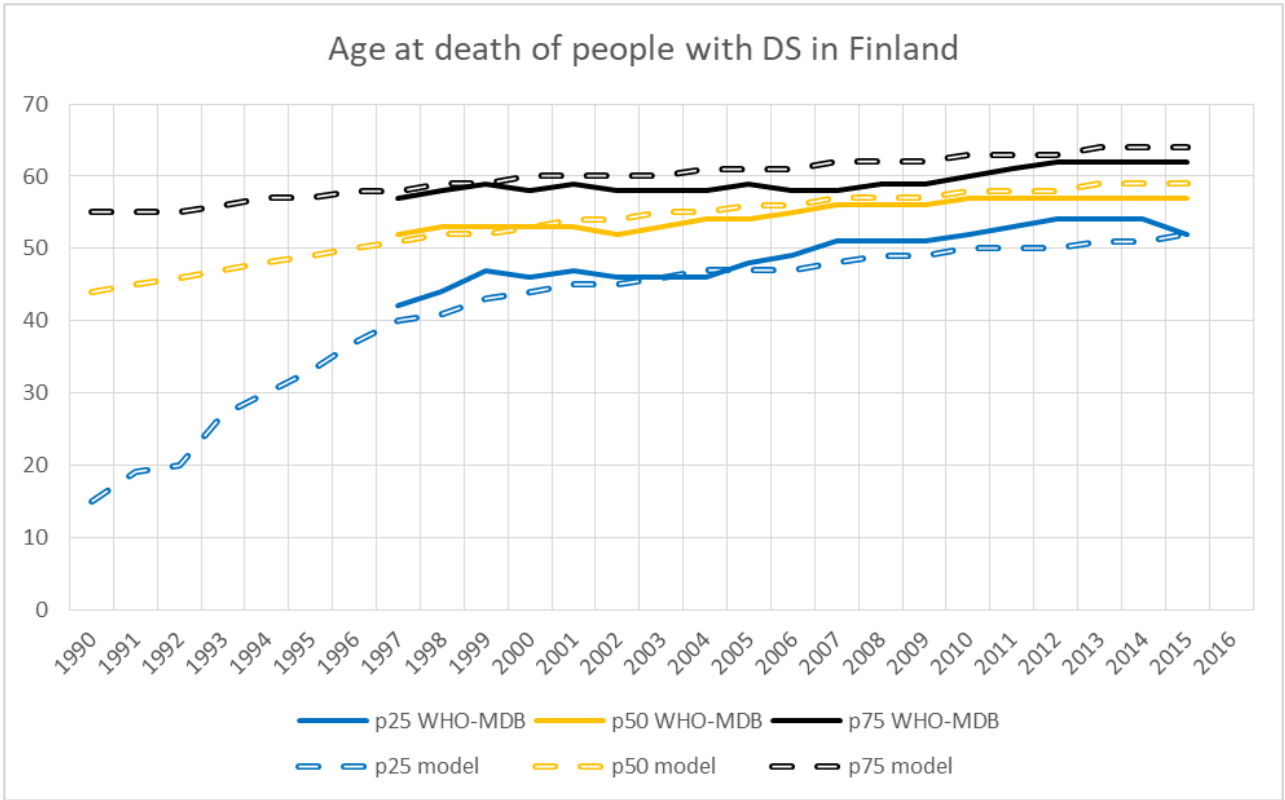

Distribution of age at death of people with DS in Denmark, 1994-2004 and 2005-2015
30%
25%
20%
15%
10%
5%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
1994-2004 national statistics (WHO-MDB)
2005-2015 national statistics (WHO-MDB)
1994-2004 model
2005-2015 model


Age at death of people with DS in Denmark
70
60
50
40
30
20
10
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model
p50 model
p75 model

Finland

The WHO Mortality Database has data available for 1996–2016. The MDB contains data on 489 people with DS who died between 2005–2015, which is 46% of the number projected by the model for the same period. For 1996–2006, it is 183 and 21%, respectively**.** For 2005–2015, correlation between MDB and model is 0.94 ($p < 0.000$); for 1996–2006, it was 0.95 ($p < 0.000$).



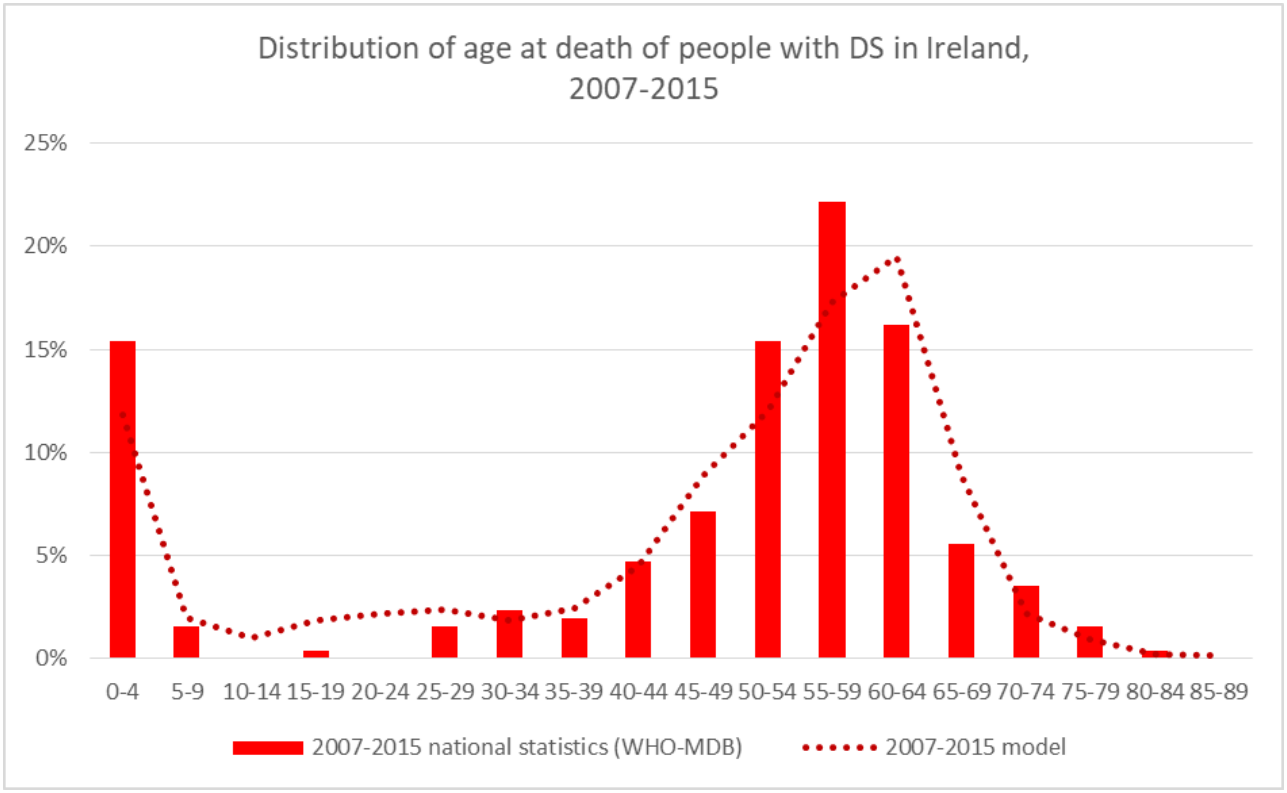


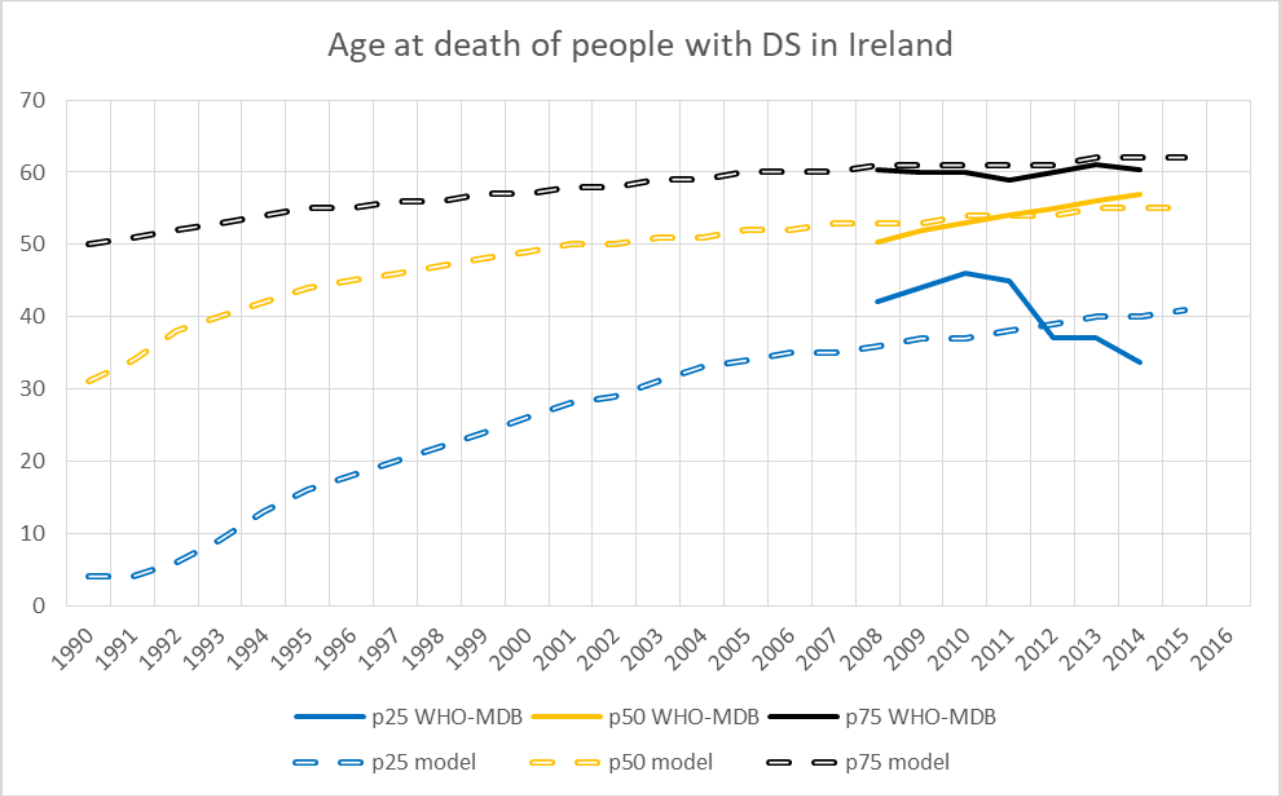
Iceland

The WHO Mortality Database reports data on DS as cause of death for 1997–2017. In total 14 deaths are reported for the period 2005–2015, 31% of what the model predicts for the same years. For 1997–2007, there were 14 reported deaths, too, 38% of the model's prediction. However, numbers in the MBD are so low that looking at the age distribution would not be purposeful.

Ireland

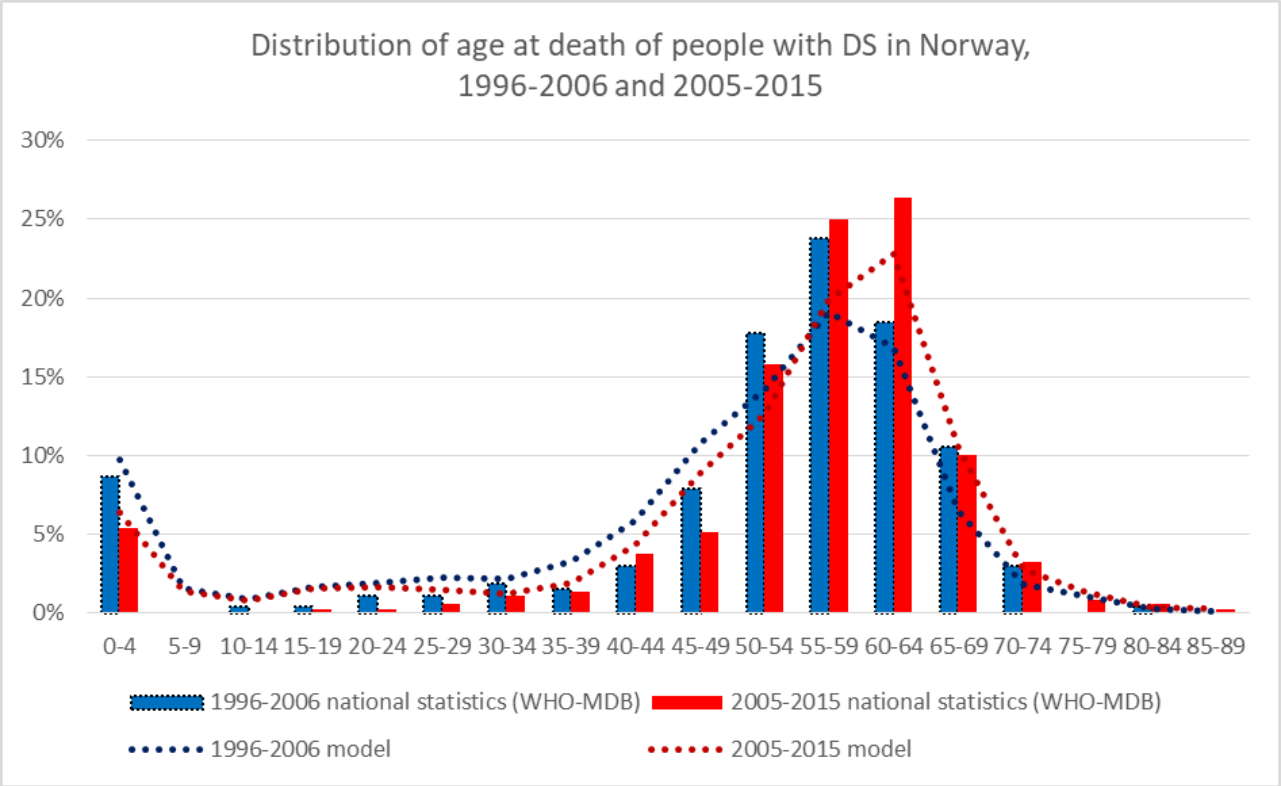
The WHO Mortality Database has data available for 2007–2015. The MDB contains data on 253 people with DS who died between 2007–2015, which is 29% of the number projected by the model for the same period. For 2007–2015, correlation between MDB and our model is 0.95 ($p < 0.000$).

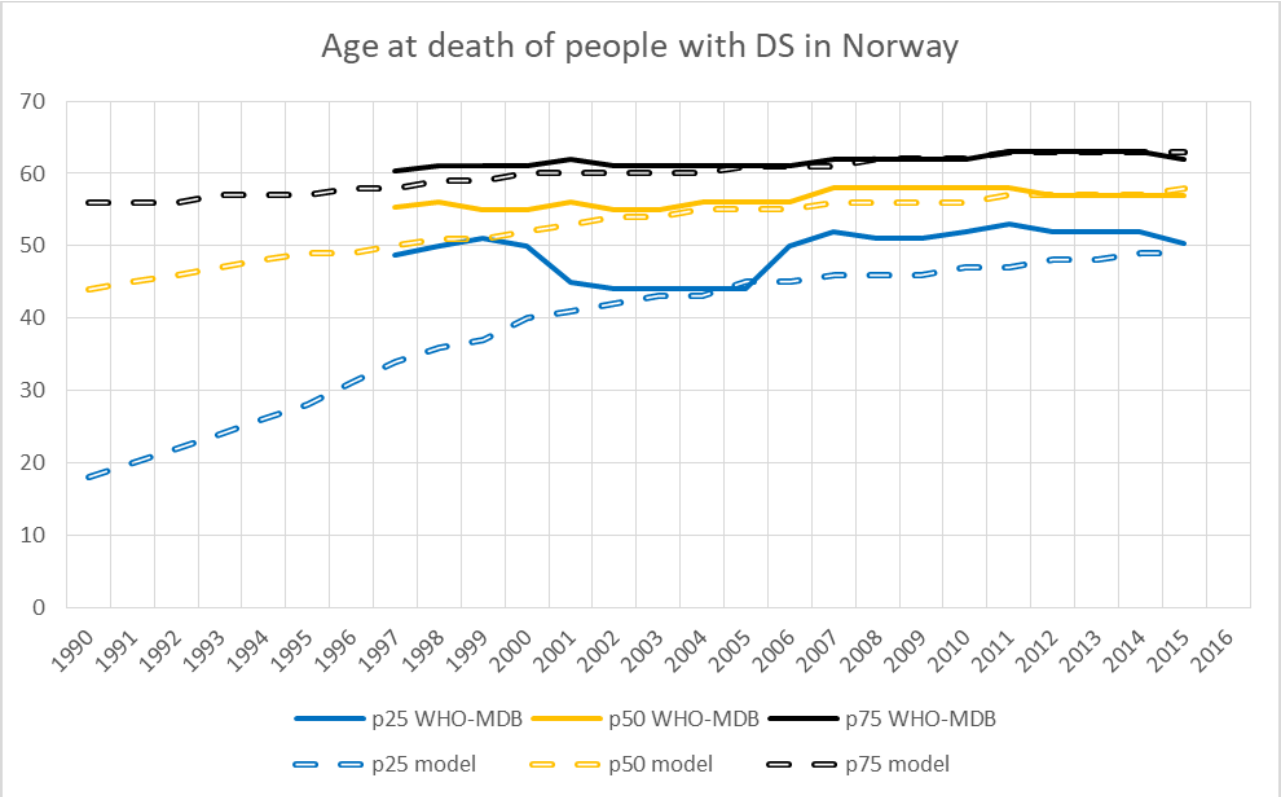




Norway

The WHO Mortality Database has data available for 1996–2016. The MDB contains data on 368 people with DS who died between 2005–2015, which is 45% of the number projected by the model for the same period. For 1996–2006, it is 265 and 41%, respectively**.** For 2005–2015, correlation between MDB and our model is 0.98 ($p < 0.000$); for 1996–2006, it was 0.97 ($p < 0.000$).

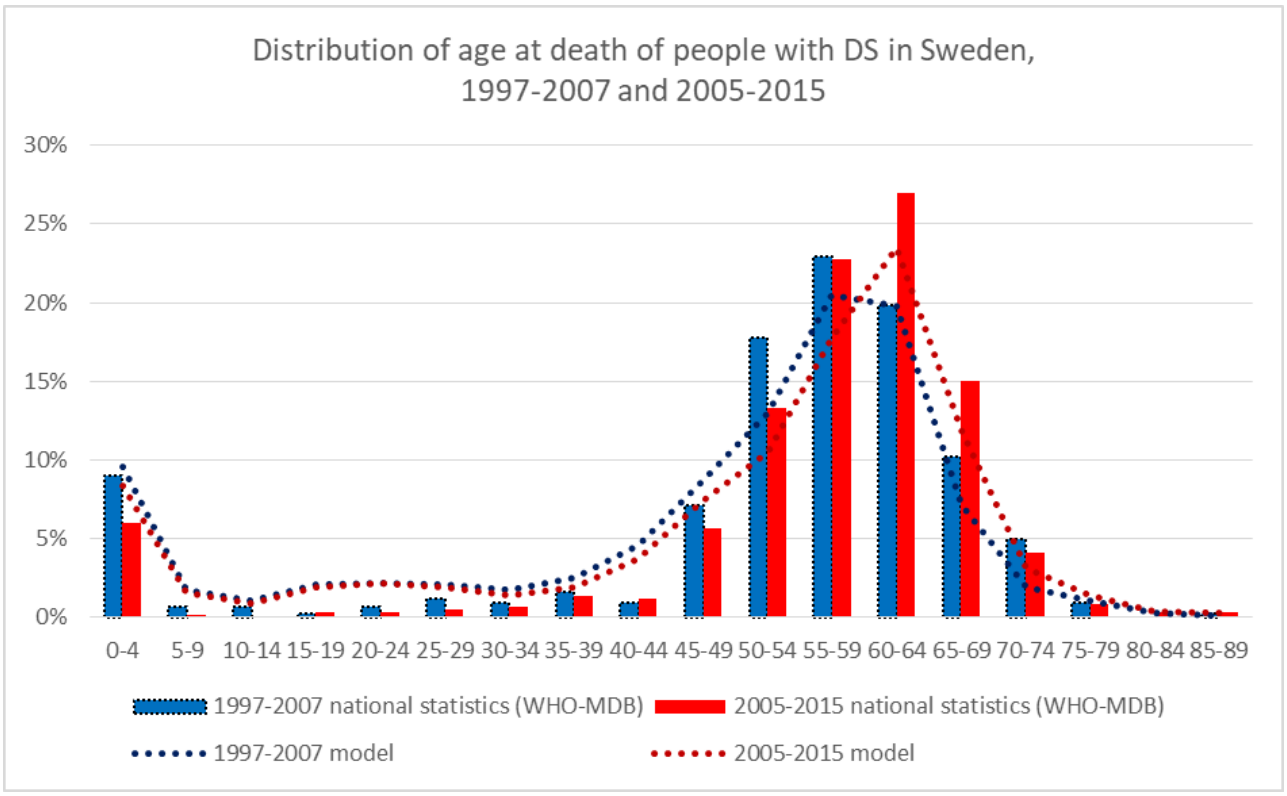


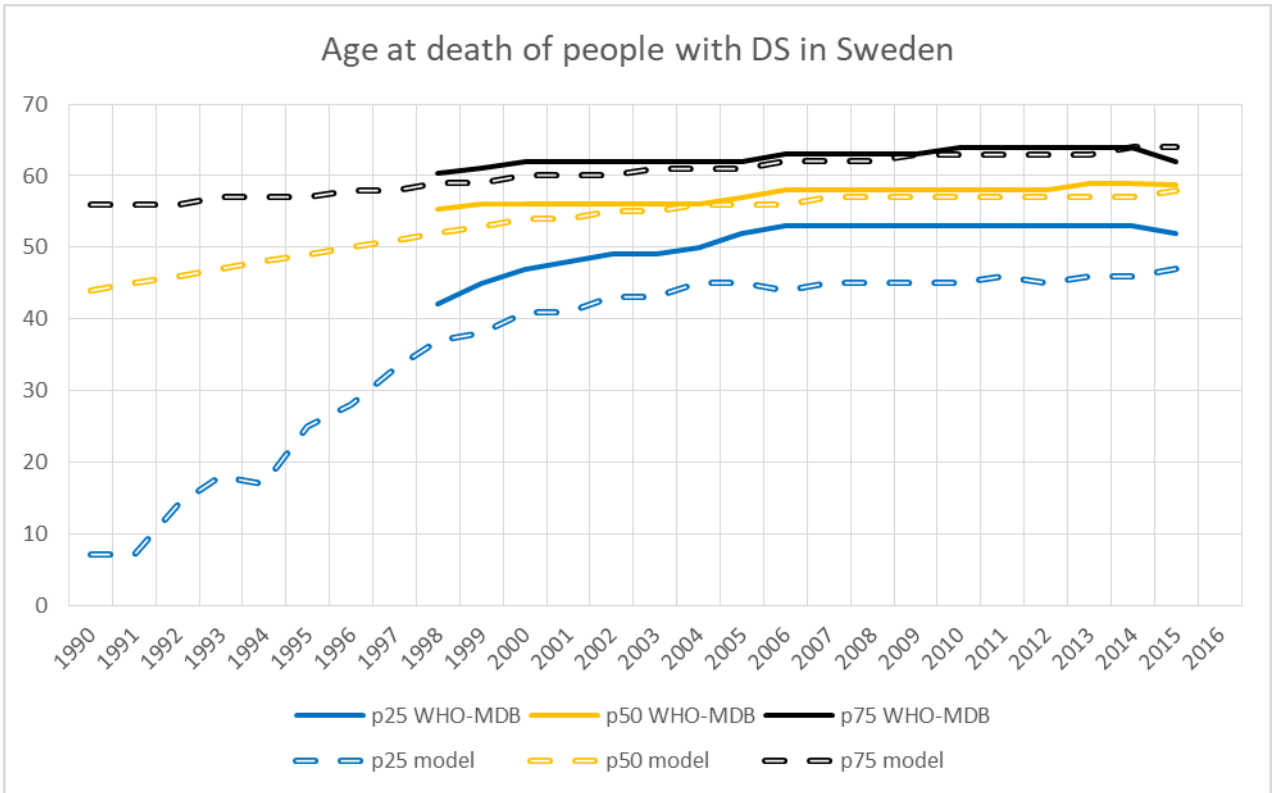


Sweden

The WHO Mortality Database has data available for 1997–2016. The MDB contains data on 585 people with DS who died between 2005–2015, which is 44% of the number projected by the model

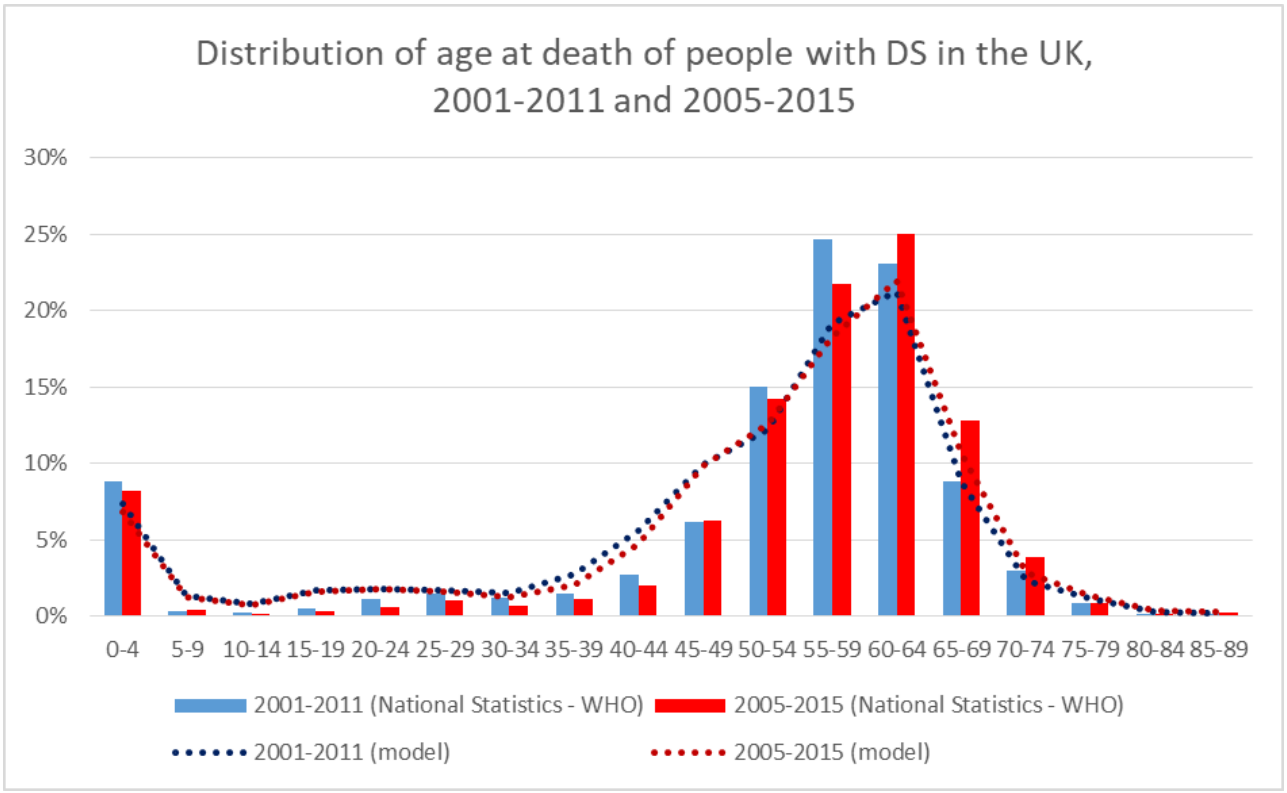
for the same period. For 1997–2007, it is 423 and 37%, respectively. For 2005–2015, correlation between MDB and model is 0.98 ($p < 0.000$); for 1997–2007, it is 0.97 ($p < 0.000$).

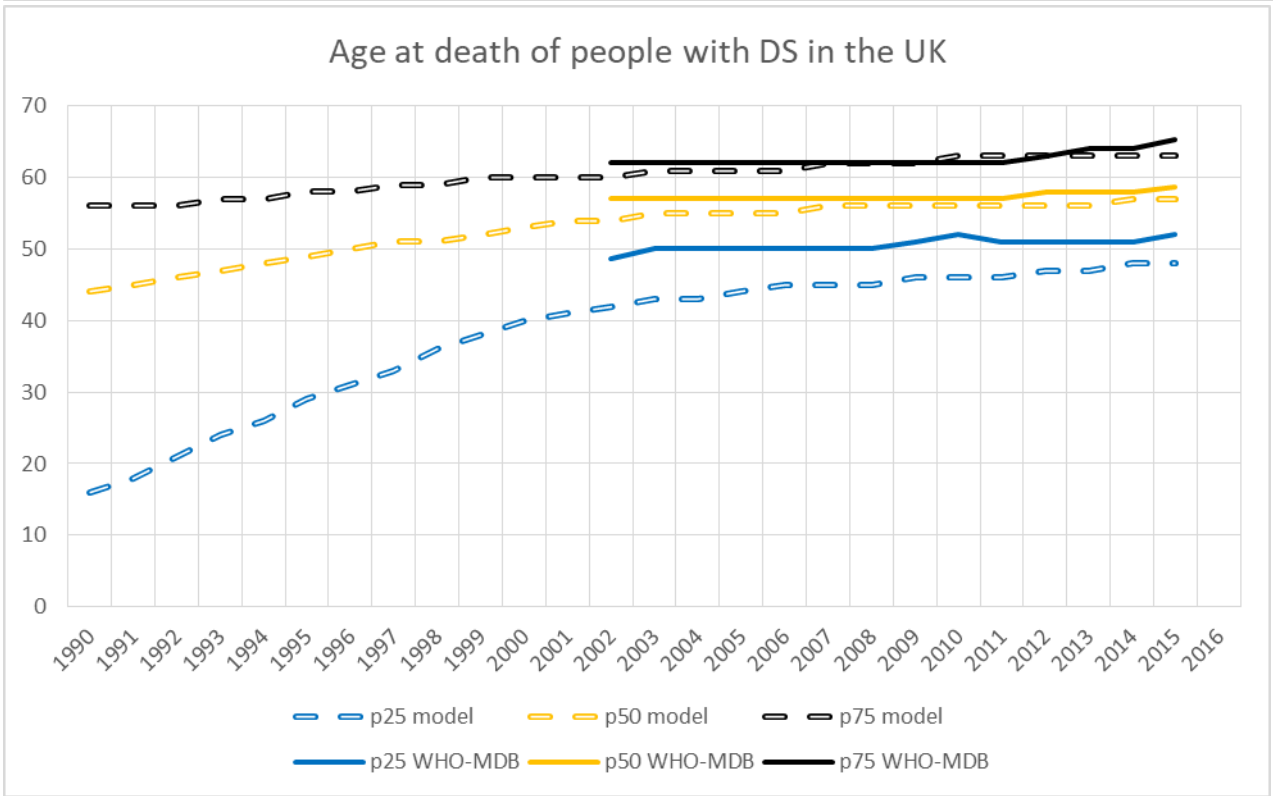




United Kingdom

The WHO Mortality Database has data available for 2001–2016. The MDB contains data on 3,181 people with DS who died between 2005–2015, which is 36% of the number projected by the model for the same period. For 2001–2011, it is 2,751 and 34%, respectively. For 2005–2015, correlation between MDB and model is 0.98 ($p < 0.000$); for 2001–2011, it was 0.98 ($p < 0.000$).

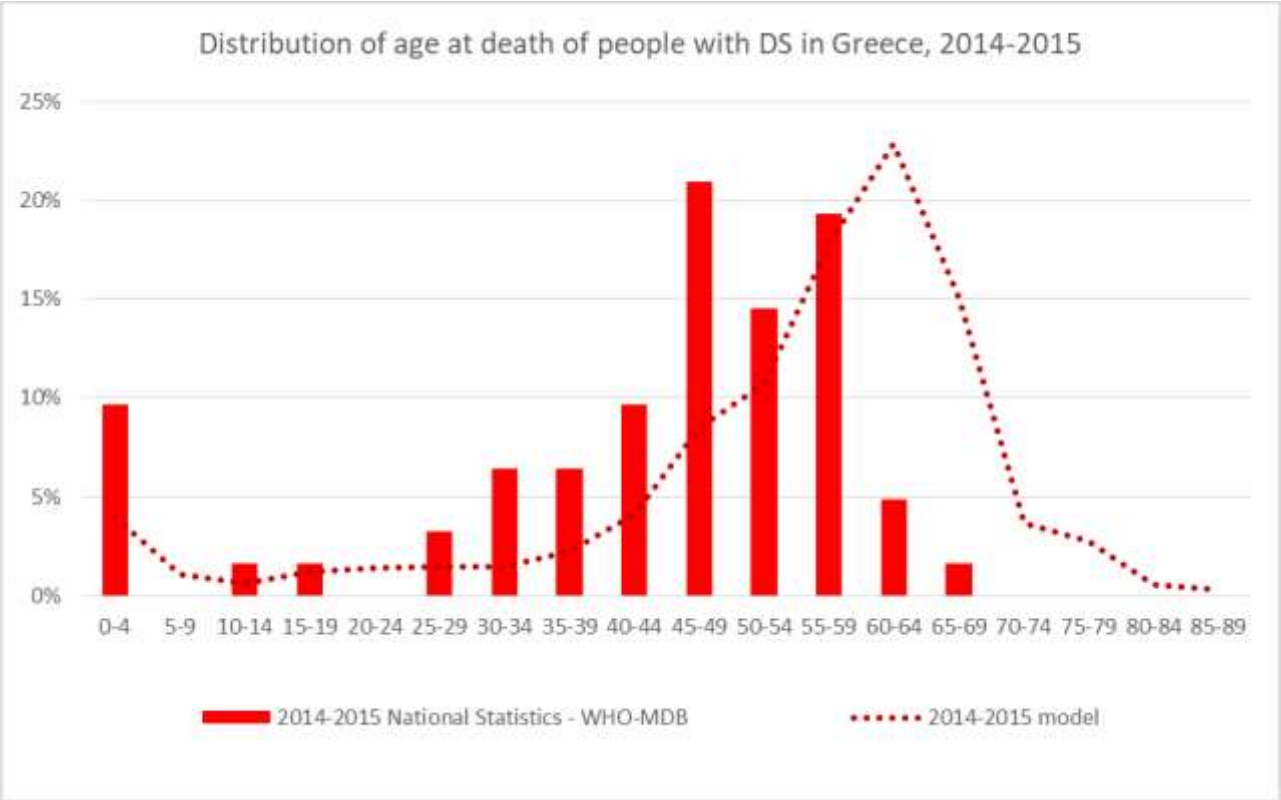




Southern Europe

Greece

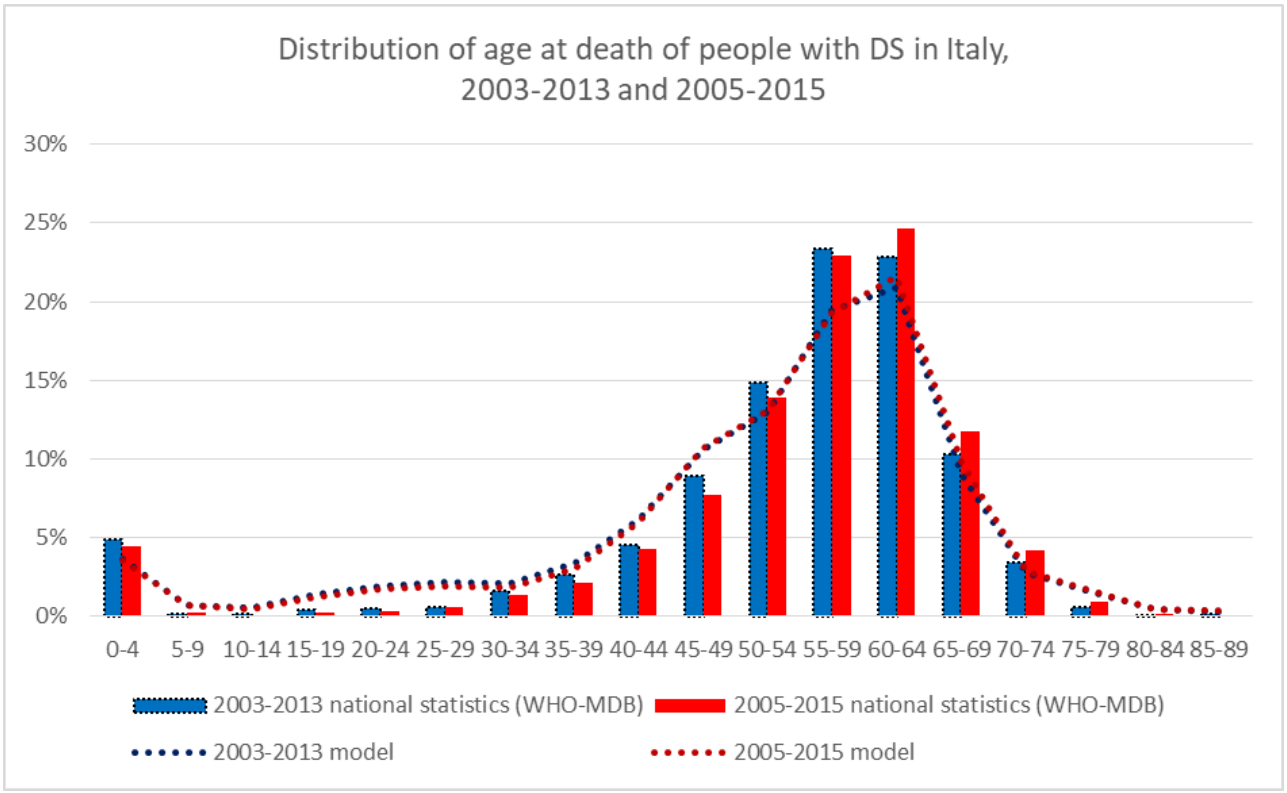
The WHO Mortality Database has data available for 2014–2016. The MDB contains data on 62 people with DS who died between 2014–2015, which is 41% of the number projected by our model for the same period. In the graph, we have added the MDB data for 2016 (69 persons) to have a more robust total number. For 2014–2015/2016, correlation between MDB and model is 0.75 ($p < 0.000$), which is lower than for any of the other former West bloc countries. Interestingly, if we had used only the 2016 Greek MDB-data, correlation would have been 0.88 ($p < 0.000$) (and the corresponding graph has a much better fit above 60 years of age), which suggests that the deceased people with DS above 60 years of age missing in the graph below—as there are only data from very few years available—might be the result of a random fluctuation in the reported numbers.

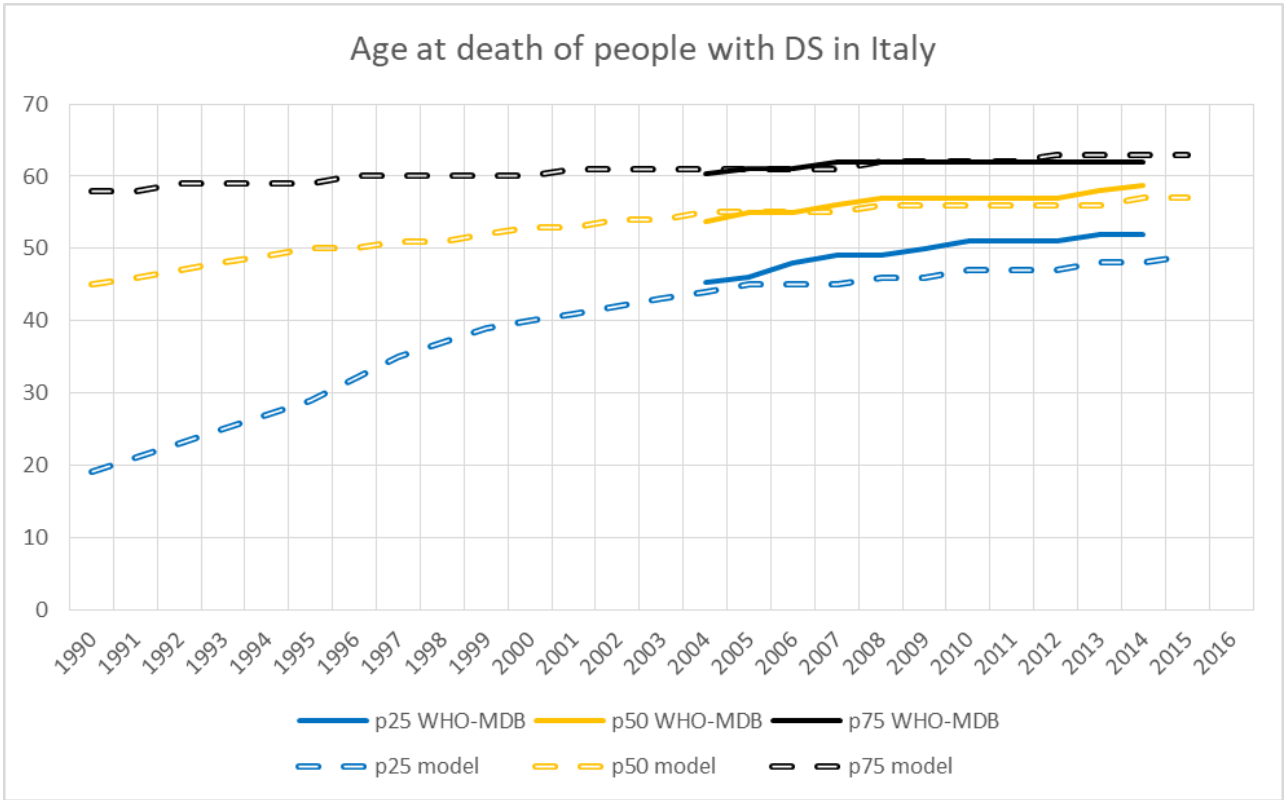


As the range of years is very short (only 3 years), we will forgo the graph depicting the 25th, 50th, and 75th percentiles of age at death.

Italy

The WHO Mortality Database has data available for 2003–2015. The MDB contains data on 2,139 people with DS who died between 2005–2015, which is 25% of the number projected by the model for the same period. For 2003–2013, it is 1,947 and 24%, respectively**.** For 2005–2015, correlation between MDB and model is 0.99 ($p < 0.000$); for 2003–2013, it is 0.99 ($p < 0.000$).



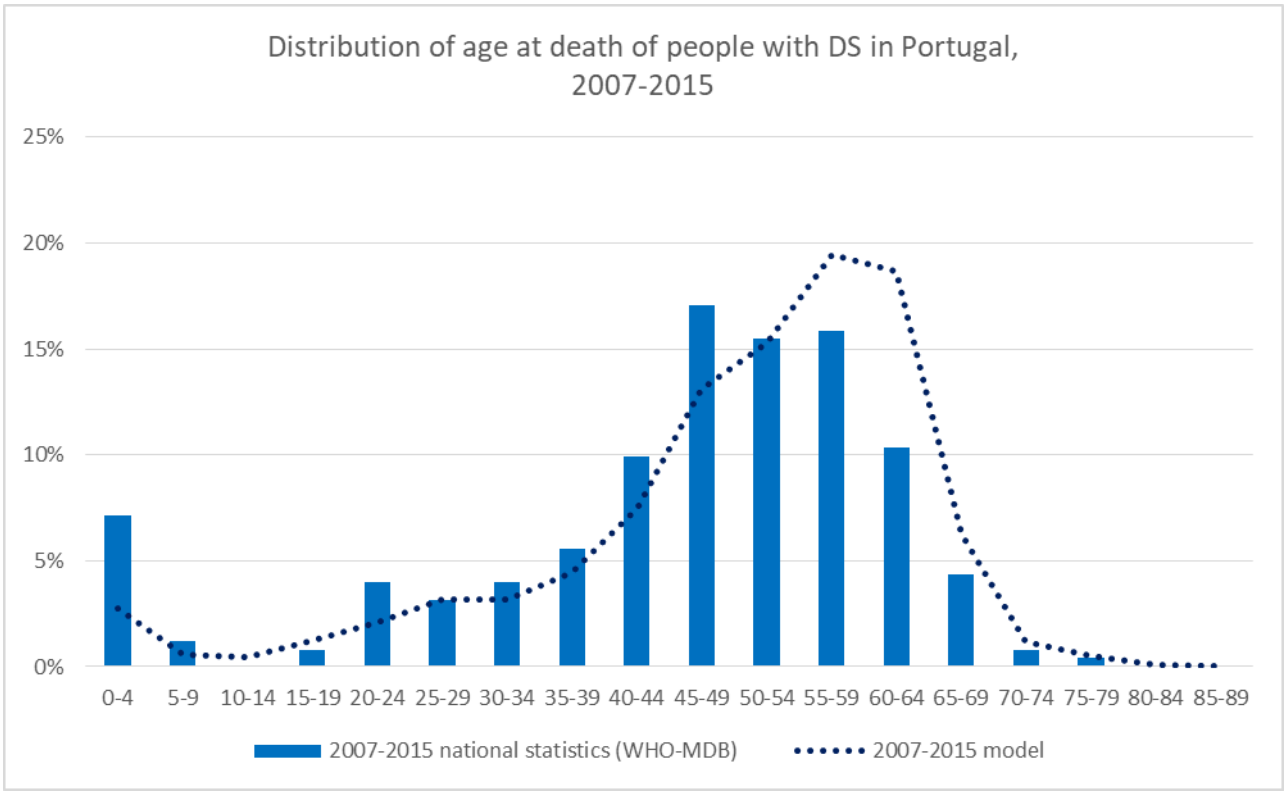


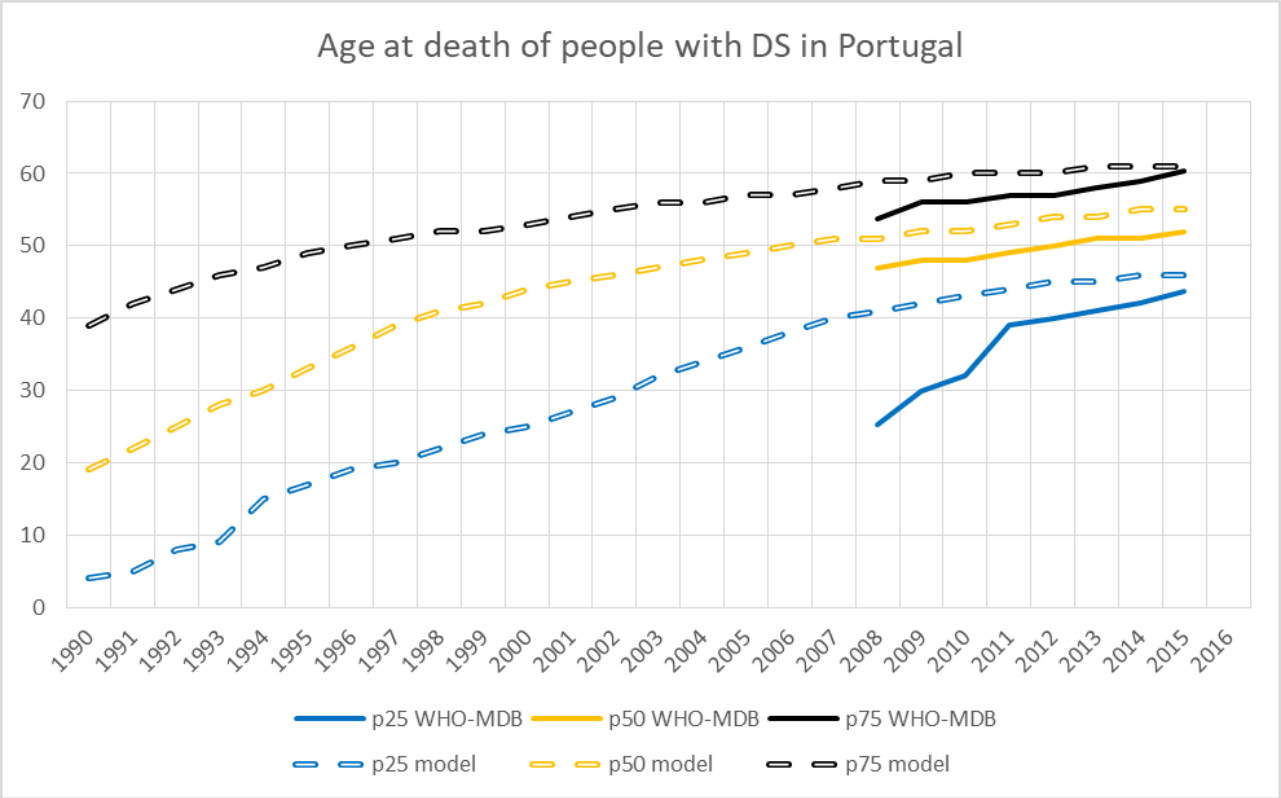
Malta

The WHO Mortality Database reports data on DS as cause of death for Malta for 1997–2015. In total, 15 deaths are reported for 2005–2015, 17% of what the model predicts for the same years. However, these are such small numbers that looking at the age distribution would not be purposeful.

Portugal

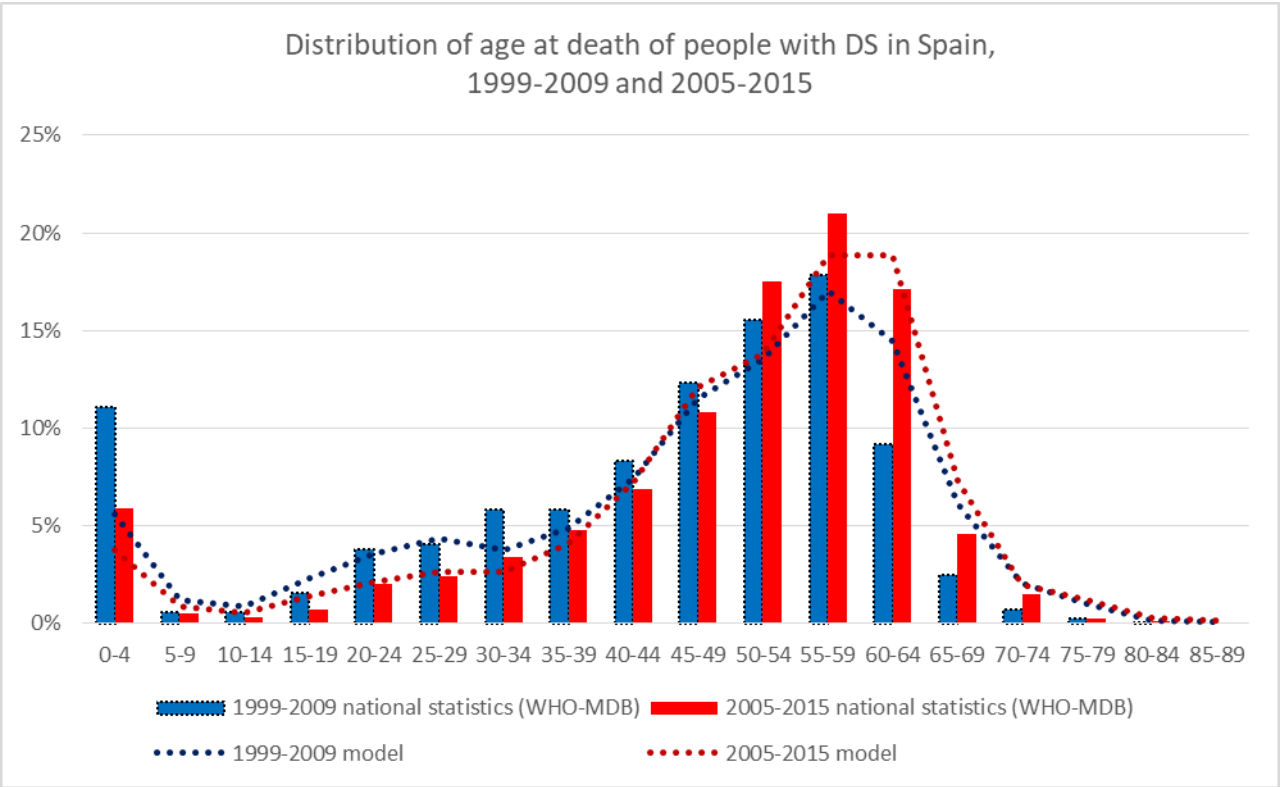
The WHO Mortality Database has data available for 2007–2015. The MDB contains data on 252 people with DS who died between 2007–2015, which is 26% of the number projected by the model for the same period. For 2007–2015, correlation between MDB and model is 0.900 ($p < 0.000$).

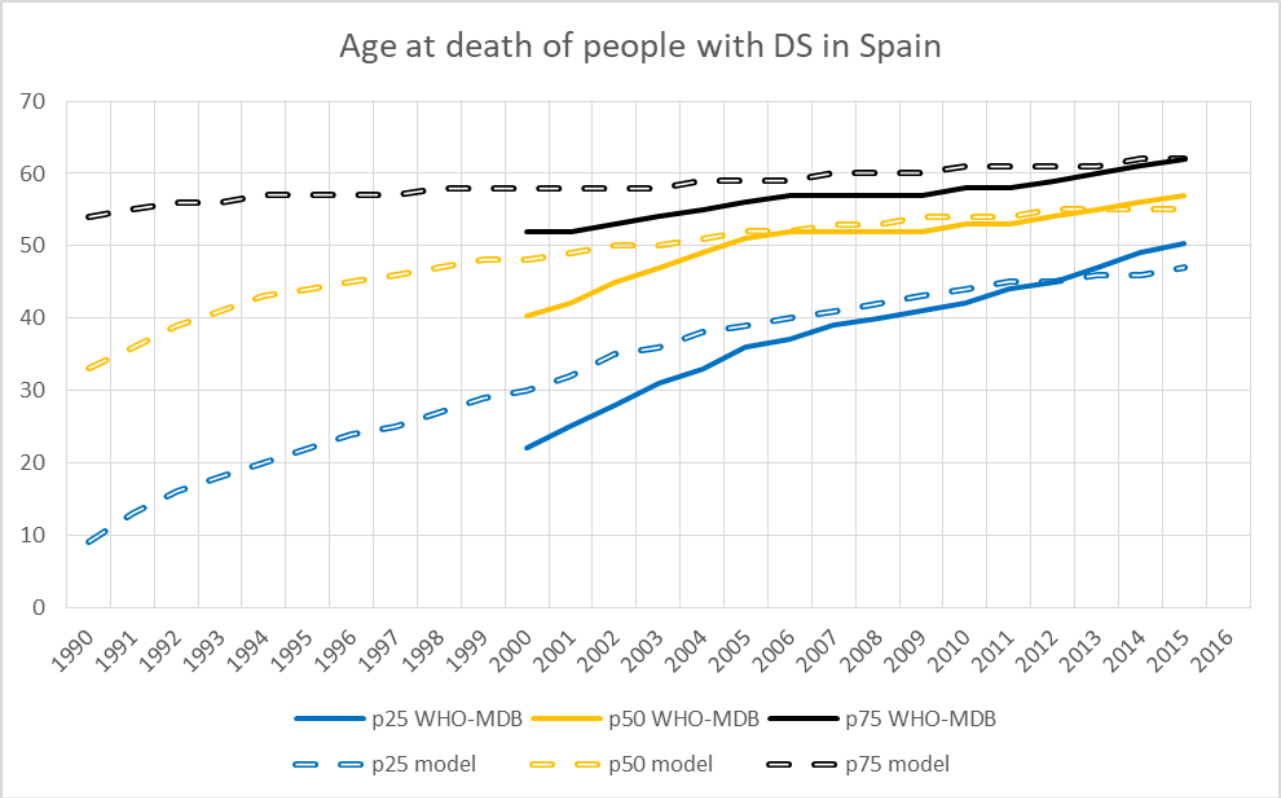




Spain

The WHO Mortality Database has data available for 1999–2016. The MDB contains data on 1,408 people with DS who died between 2005–2015, which is 23% of the number projected by the model for the same period. For 1999–2009, it is 1,166 and 24%, respectively. For 2005–2015, correlation between MDB and our model is 0.98 ($p < 0.000$); for 2003–2013, it is 0.92 ($p < 0.000$).

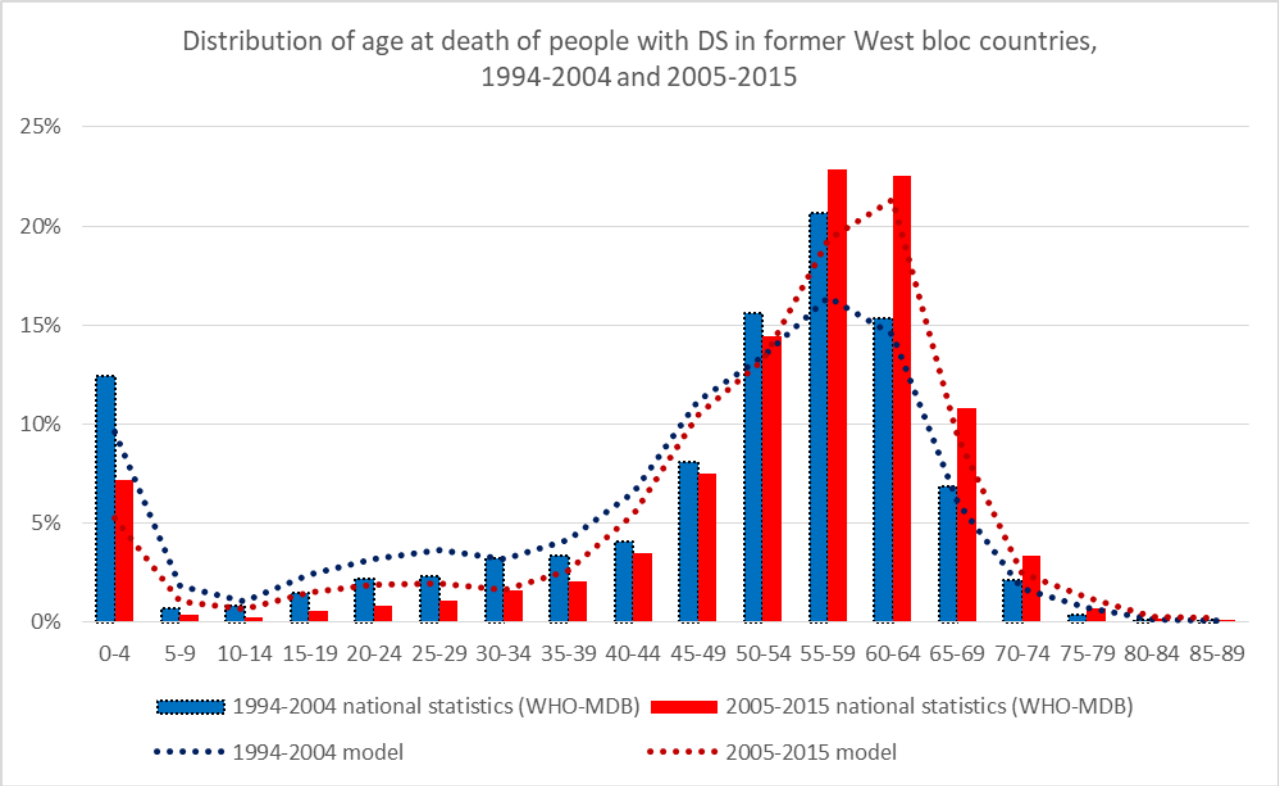




All the former West bloc countries pooled

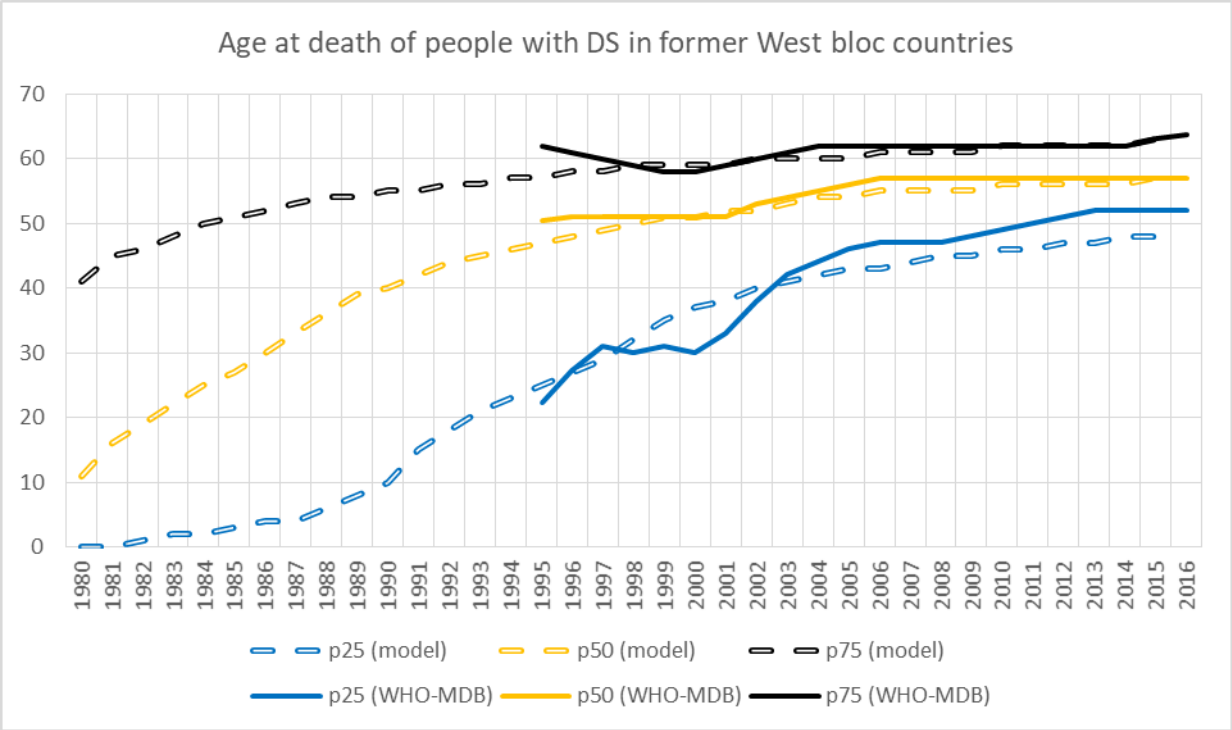
To further explore the data and to compare later on with the situation in former East bloc countries, we have pooled the data for all the former West bloc countries for 2005–2015 and for the older range of years (1994–2004, or if 1994 was not available, 1995–2005, etc.).

Pooled for 2005–2015, the MDB has information on 19,000 deceased people with DS in former West bloc countries, which is 36% of the number predicted by the model. For 1994–2004, this is 8,600, which is 17% of the model's projection (but the MDB does not contain information on all these countries for all the years of birth in this period). Looking at the graph below, there appears to be a good fit between model and MDB. For 2005–2015, in regards to the age distribution of deceased people with DS, the correlation between MDB and the model is 0.98 ($p < 0.000$). For 1994–2004, it is 0.97 ($p < 0.000$).



If we look at the age distribution of only people with DS who are 10 years of age and older, the correlation between MDB and our model is 0.99 ($p < 0.000$) for 2005–2015 and 0.97 ($p < 0.000$) for 1994–2004. If we look at only people with DS up to 55 years of age, it is 0.95 ($p < 0.000$) for 2005–2015 and 0.95 ($p < 0.000$) for 1994–2004.

The graph below presents the age at death of people with DS in former West bloc countries, showing a good fit between our model and MDB.



Countries from the former East bloc

Below, we will present the data from the former East bloc countries. For 4 of these countries (Albania, Belarus, Russia, and Ukraine), no data on DS are available in the WHO Mortality Database (MDB). For 2 countries (Bosnia and Herzegovina; Montenegro), numbers of deceased people with DS in the MDB are so low, that it would not be purposeful to make a comparison with our model. For the other 14 countries, a comparison was possible. For most countries, it was possible to compare two rows of years—that is, 2005–2015 and a period starting with the first available year in the MDB (for instance, 1995–2005).

For most comparisons, there is not a good fit of model A with the MDB in regards to the age distribution of deceased people with DS. Only for 2 comparisons the correlation between model A and MDB is above 0.9—that is, for Serbia (1998–2008) and Slovenia (2005–2015). For 7 comparisons, the correlation is moderate—that is, between 0.7–0.9. For 17 other comparisons, it is below 0.7. Model B, the model with a lower survival before 2000 (modeled for all age groups), has a better fit in regards to the age distribution. For 11 comparisons, the correlation is above 0.9. For 15 comparisons, it is between 0.7 and 0.9, and for none of the comparisons is it below 0.7. Model C (with a lower survival before 1980–1985, but only for the groups above 10 years of age) has 10 comparisons above 0.9, 8 comparisons between 0.7–0.9, and 8 comparisons below 0.7. Model D (the middle of B and C) has 13, 8, and 5 comparisons, respectively. Model B, and to a lesser extent Model D, have a better fit (for most of the countries) with the MBD data than model A.

An average of 77% the deceased people with DS (range 63–90%) in the MDB data were 45–70 years of age in the former West bloc countries for the period 2005–2015. In contrast, an average of only 39% of the deceased people with DS (range 2–74%) were 45–70 years of age in the former East bloc countries for the period 2005–2015. In the former West bloc countries, the lowest value was 63%; out of the former East bloc countries, only Slovenia had a value above 63%.

For the former East bloc countries, for 2005–2015, our initial model predicts 66% (range 45-79%) of deceased people with DS to be in the 45–70 year age group, which is way above the average of 39% (range 2–74%) found in the MDB data. For these countries, Model B predicts an average of 42% (range 19–62%). Model C predicts 55% (38–69%), and Model D predicts 52% (30–69%). In this regard, Model B has the best fit, followed by Model D.

For 2005–2015, Pearson correlation between MDB percentages by country and model A is 0.65 ($p < 0.012$). (A higher correlation implies that a higher percentage in the MDB data of people in the age range 45–70 years is matched by a higher percentage in this age range from the predictions.) For Model B, it is 0.75 ($p < 0.002$). For Model C, it is 0.6 ($p < 0.023$), and for Model D, it is 0.79 ($p < 0.001$). In this regard, Model D has the best fit, followed by Model B.

For the older range of years (1994–2004, or if 1994 was not available for a specific country, 1995-2005, etc.), an average of 72% of the deceased people with DS (range 57–80%) in the MDB data were 45–70 years of age in the former West bloc countries. In contrast, in the former East bloc countries, the corresponding value is, on average, only 19% (range 0–36%). Where in the former West bloc countries, the lowest value was 57%, in the former East bloc countries, the highest value was 36%. As such, there is a very consistent and distinctive difference between former East bloc and former West bloc countries in the MDB data.

For the former East bloc countries, for the older range of years, the initial model (Model A) predicts 53% (range 28–75%) of deceased people with DS were 45–70 years old, which is way above the average of 19% (range 0–36%) found in the MDB data. Model B predicts 24% (range 9–47%). Model C

predicts 35% (21–55%), and Model D predicts 32% (17–54%). In this regard, Model B has the best fit, followed by Model D. Pearson correlation between MDB and model A (the initial model) for percentages between 45–70 years of age by country is 0.46 ($p < 0.14$). For Model B, it is 0.55 ($p < 0.062$). For Model C , it is 0.49 ($p < 0.106$), and for Model D, it is 0.61 ($p < 0.035$). In this regard, Model D has the best fit, followed by model B.

Below, we will analyze by country. Finally, we will look at the data for all former East bloc countries together.

Northern Europe

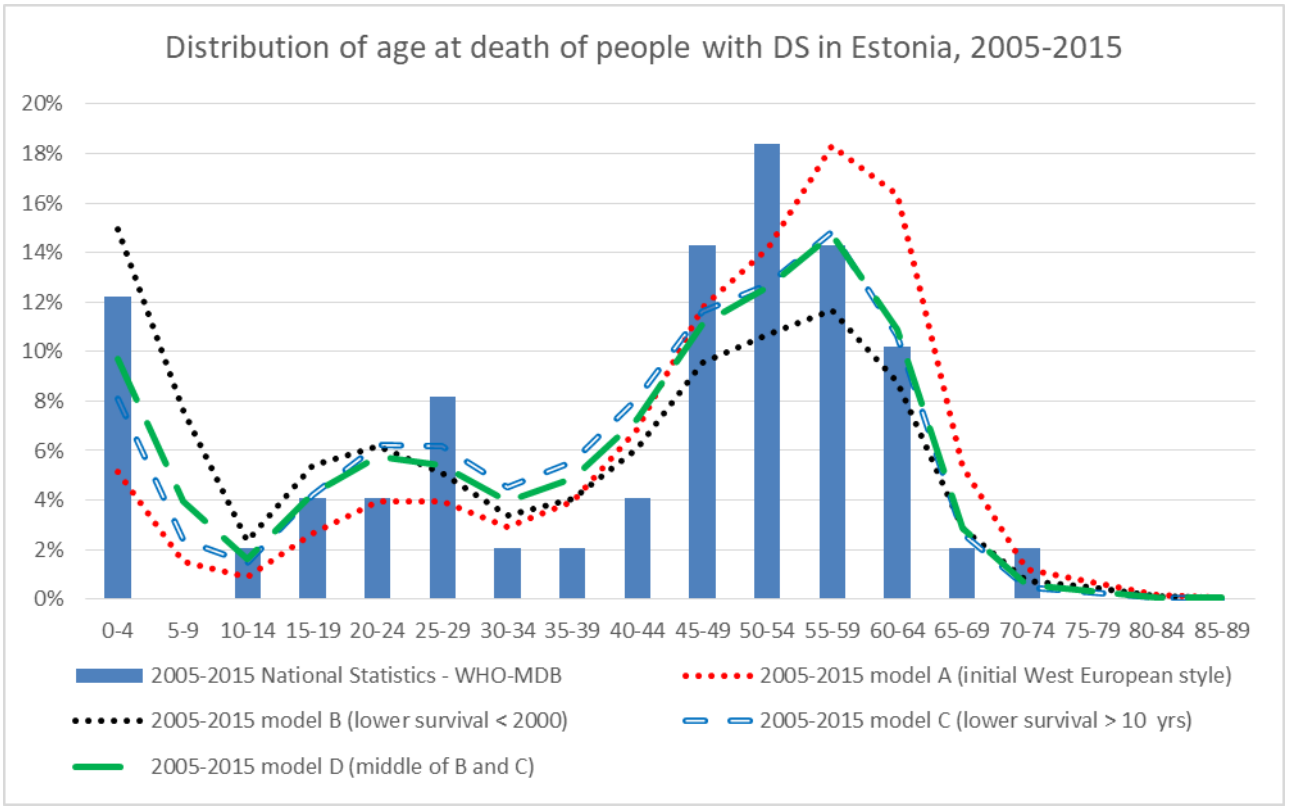
Estonia

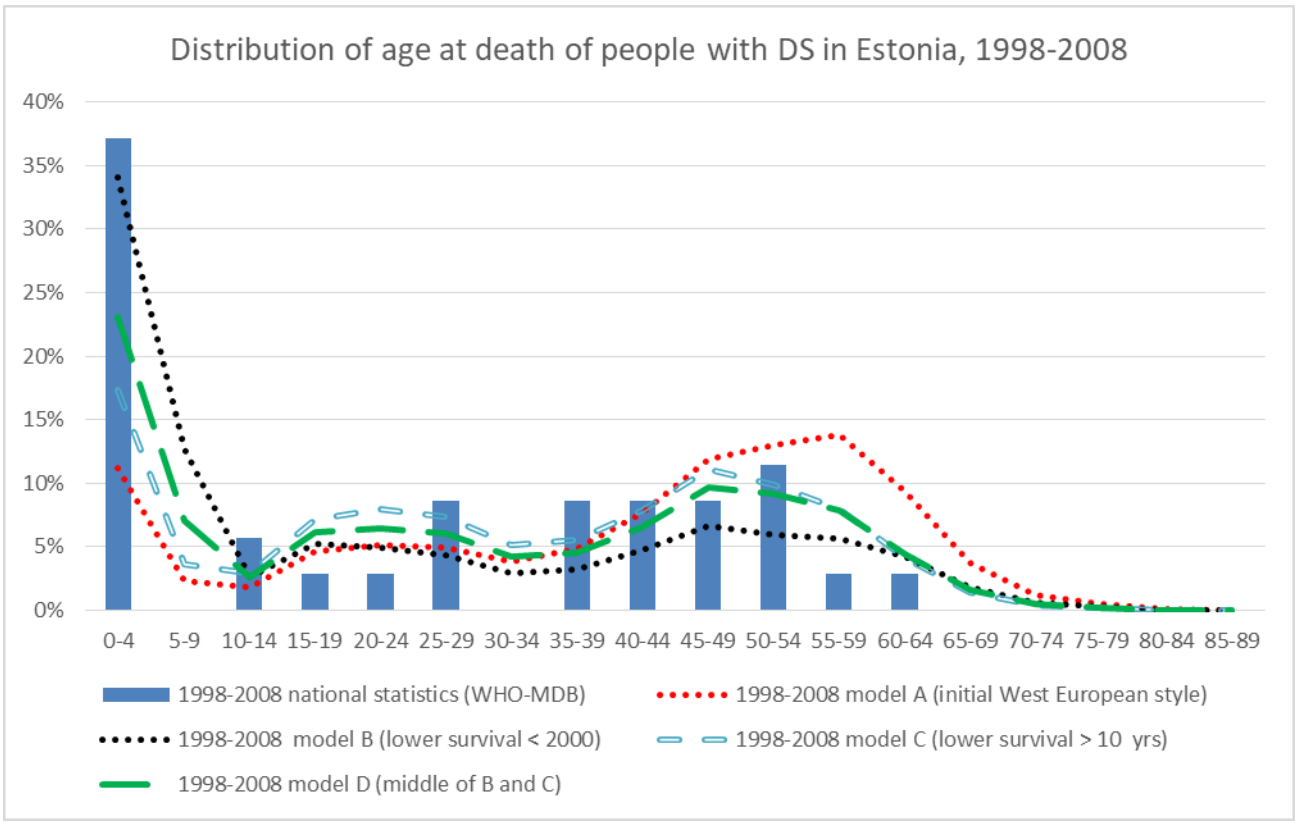
For Estonia, the WHO Mortality Database has data available for 1998–2015. The MDB contains data on 49 people with DS who died between 2005–2015, which is 35% of the number projected by Model A (West-European like survival) for the same period, 102% of the number projected by the adapted Model B with a lower survival before 2000 (modeled for all age groups), 56% of the alternative Model C (with a lower survival before 1980, but only for the groups above 10 years of age), and 67% of Model D (the middle of B and C). For 1998–2008, this is 35 people, 33% of the projection of model A, 75% of Model B, 51% of Model C, and 58% of Model D. The 102% for Model B for 2005–2015 makes this model unlikely, as it is improbable that everyone with DS who dies is registered as having died with DS as primary cause of death. We do not believe that the cause of this phenomenon in Estonia is that we have modeled too low of a mortality in the age group 0–4 years. If the absolute number of deceased persons with DS in the MBD for this age range would have been higher than predicted by the models, this would imply that mortality for this age range had been modeled too low; however, this is not the case in Estonia.

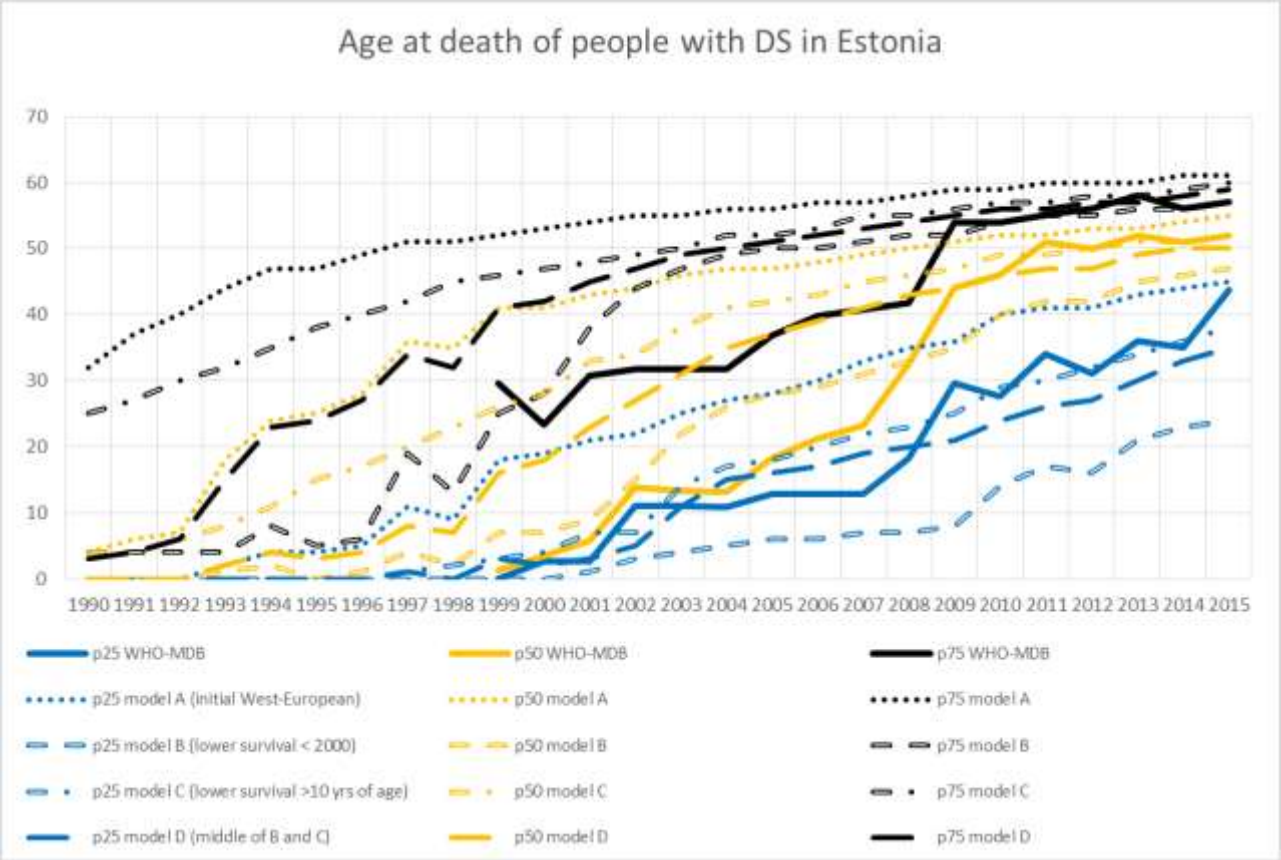
Looking at the graphs, the best fitting model seems to be Model C or Model D, with Model D fitting better in regards to the percentage in the 0–4 year age group. In addition, we think that a model that assumes a poorer survival, but only for those above 10 years of age, is not fully credible. Model A has the poorest fit.

For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and Model A is 0.85 ($p < 0.000$). Correlation of MDB with Model B is 0.83 ($p < 0.000$), with Model C is 0.91 ($p < 0.000$), and with Model D is 0.92 ($p < 0.000$). For 1998–2008, this is respectively 0.54 ($p < 0.022$) for Model A, 0.88 ($p < 0.000$) for Model B, 0.83 ($p <0.000$) for Model C, and 0.90 ($p < 0.000$) for Model D. Model D has the best fit.

In 2005–2015, the MDB has 59% in the age range 45–70 years. Model A has 66%, and Model B has 44%. Model C has 52%, and Model D has 52%. In 1998–2008, the MDB value is 25%. Model A predicts 52%, and Model B predicts 24%. Model C predicts 34%, and Model D predicts 33%. Model B seems to fit the 1998–2008 data best but predicts a too low value for 2005–2015.


Distribution of age at death of people with DS in Estonia, 2005-2015
20%
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
2005-2015 National Statistics - WHO-MDB
2005-2015 model A (initial West European style)
2005-2015 model B (lower survival < 2000)
2005-2015 model C (lower survival > 10 yrs)
2005-2015 model D (middle of B and C)


Distribution of age at death of people with DS in Estonia, 1998-2008
40%
35%
30%
25%
20%
15%
10%
5%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
1998-2008 national statistics (WHO-MDB)
1998-2008 model A (initial West European style)
1998-2008 model B (lower survival < 2000)
1998-2008 model C (lower survival > 10 yrs)
1998-2008 model D (middle of B and C)


Age at death of people with DS in Estonia
70
60
50
40
30
20
10
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model A (initial West-European)
p50 model A
p75 model A
p25 model B (lower survival < 2000)
p50 model B
p75 model B
p25 model C (lower survival >10 yrs of age)
p50 model C
p75 model C
p25 model D (middle of B and C)
p50 model D
p75 model D

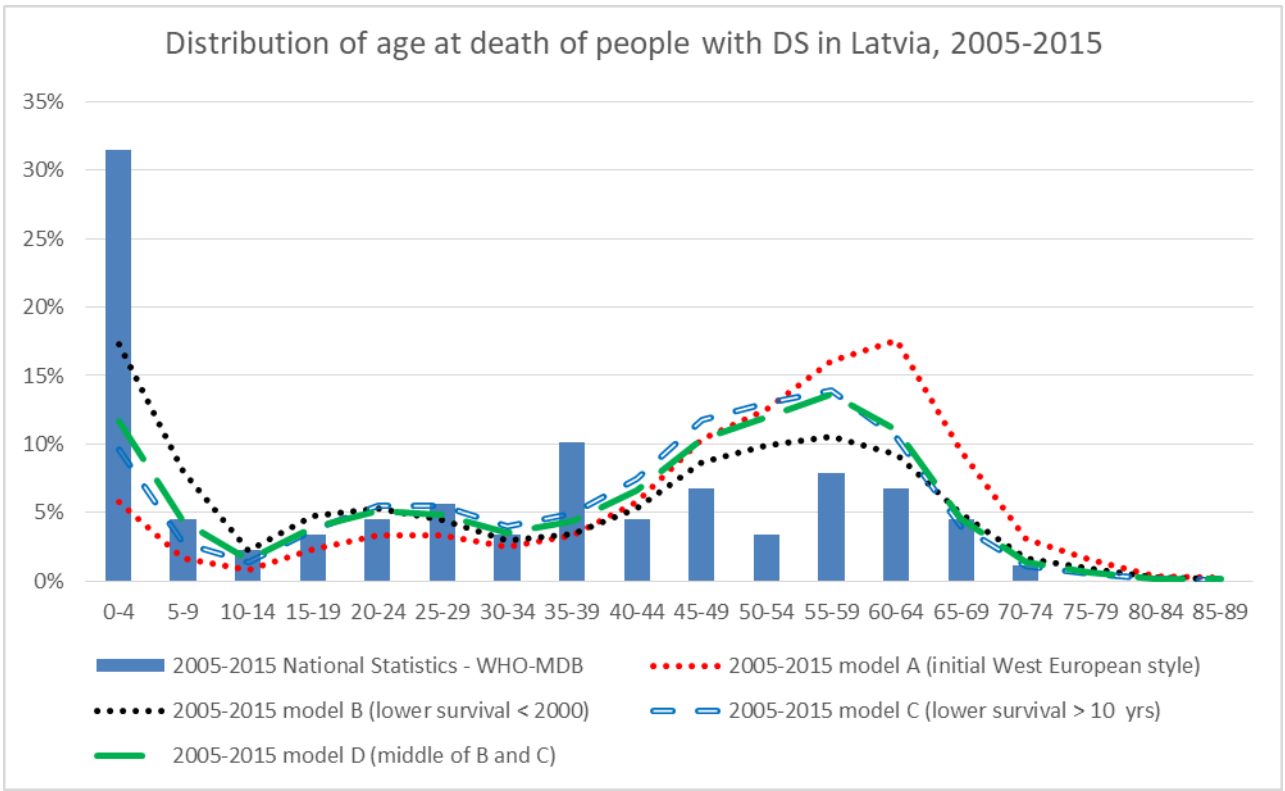
Latvia

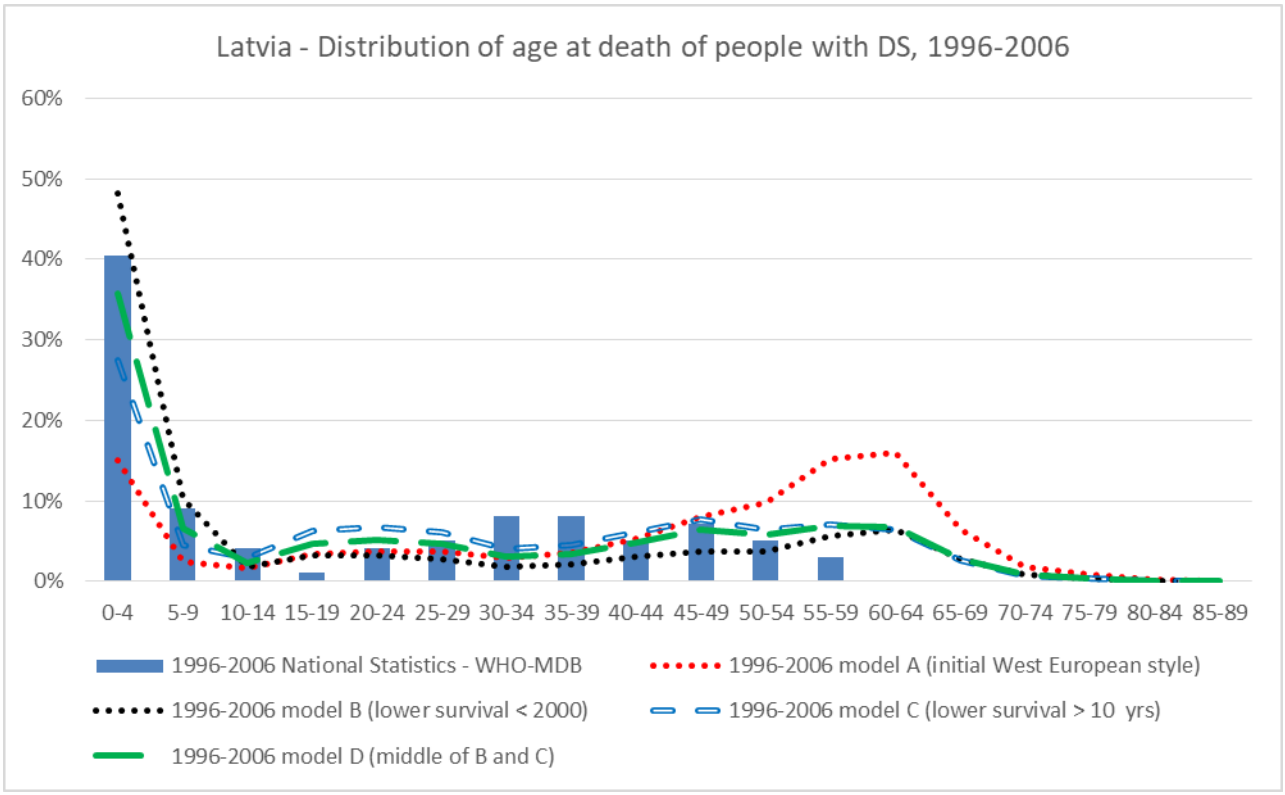
The WHO Mortality Database has data available for 1996–2015. The MDB contains data on 89 people with DS who died between 2005–2015, which is 31% of the number projected by Model A (West-European like survival) for the same period, 93% of the number projected by Model B, 52% of Model C, and 63% of Model D. For 1996–2006, this is 99 people, 41% of the projection of Model A, 78% of Model B, 75% of Model C, and 78% of Model D. The 93% for Model B for 2005–2015 makes this model unlikely, as it is improbable that almost everyone with DS who dies is registered as having died with DS as primary cause of death. However, the absolute number of children who died in the 0–4 year age group is higher in the MDB than in the models. This suggests that mortality for this age group may have been modeled too low in the models during recent years. If we limit the comparison to people with DS aged 5 years and older, for 2005–2015, the MDB contains 77% of the deaths in Model B, which is high, but not entirely impossible.

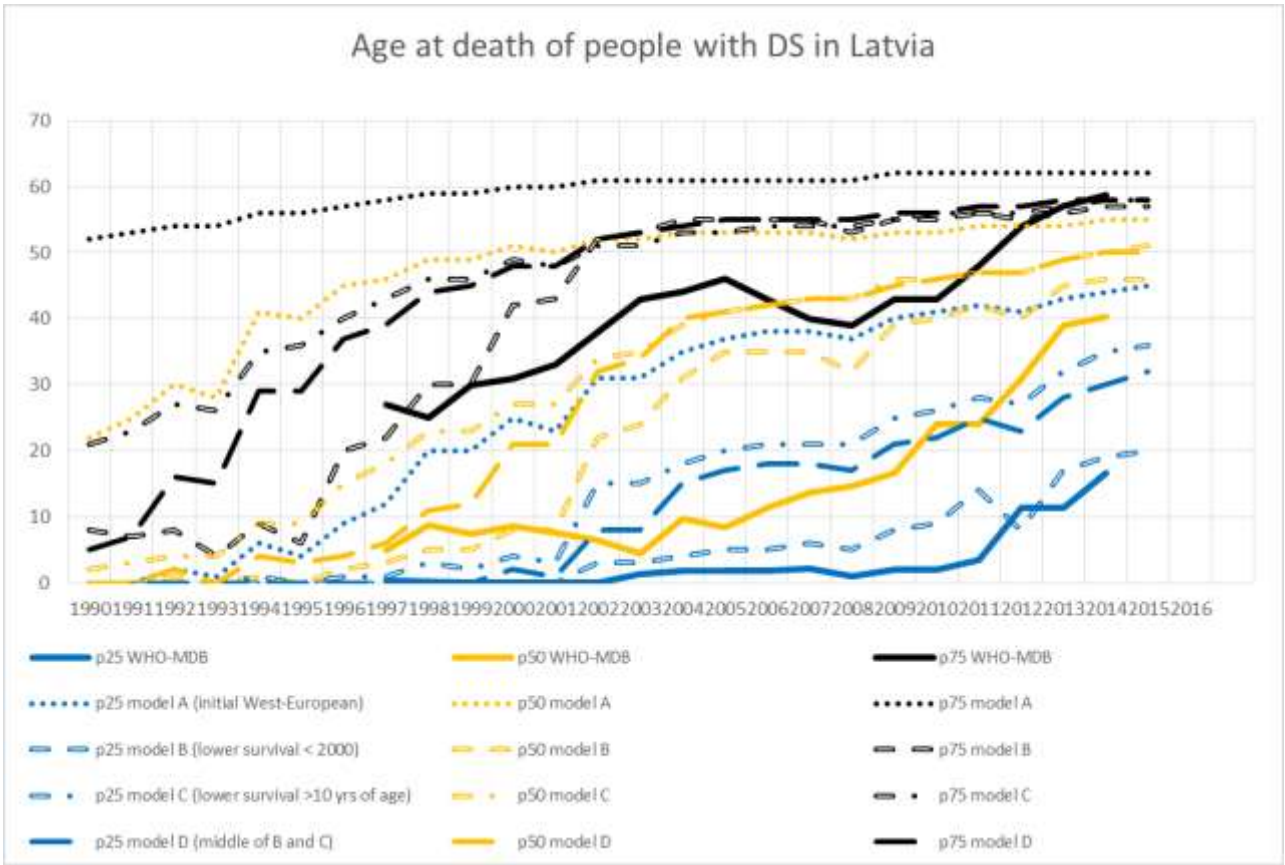
Looking at the graphs, the best fitting model seems to be Model B, C or D, of which we deem Model B less likely (as we have stated above) and Model D slightly better fitting and more credible than model C.

For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and Model A is 0.23 ($p < 0.358$). Correlation of MDB with Model B is 0.8 ($p < 0.000$). With Model C, it is 0.46 ($p < 0.054$), and with Model D it is 0.57 ($p < 0.014$). For 1996–2006, this is respectively 0.42 ($p < 0.079$) for Model A, 0.95 ($p < 0.000$) for Model B, 0.92 ($p < 0.000$) for Model C, and 0.95 ($p < 0.000$) for Model D. Model B, followed by Model D, has the best fit.

In 2005–2015, the MDB has 29% in the age range 45–70. Model A has 66%, and Model B has 43%. Model C has 53%, and Model D has 52%. In 1998–2008, the MDB value is 15%. Model A predicts 56%, Model B predicts 22%, Model C predicts 30%, and Model D predicts 28%. In this regard, Model B seems to have the best fit.




Latvia - Distribution of age at death of people with DS, 1996-2006
60%
50%
40%
30%
20%
10%
0%
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
1996-2006 National Statistics - WHO-MDB
1996-2006 model A (initial West European style)
1996-2006 model B (lower survival < 2000)
1996-2006 model C (lower survival > 10 yrs)
1996-2006 model D (middle of B and C)


Age at death of people with DS in Latvia
70
60
50
40
30
20
10
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model A (initial West-European)
p50 model A
p75 model A
p25 model B (lower survival < 2000)
p50 model B
p75 model B
p25 model C (lower survival >10 yrs of age)
p50 model C
p75 model C
p25 model D (middle of B and C)
p50 model D
p75 model D

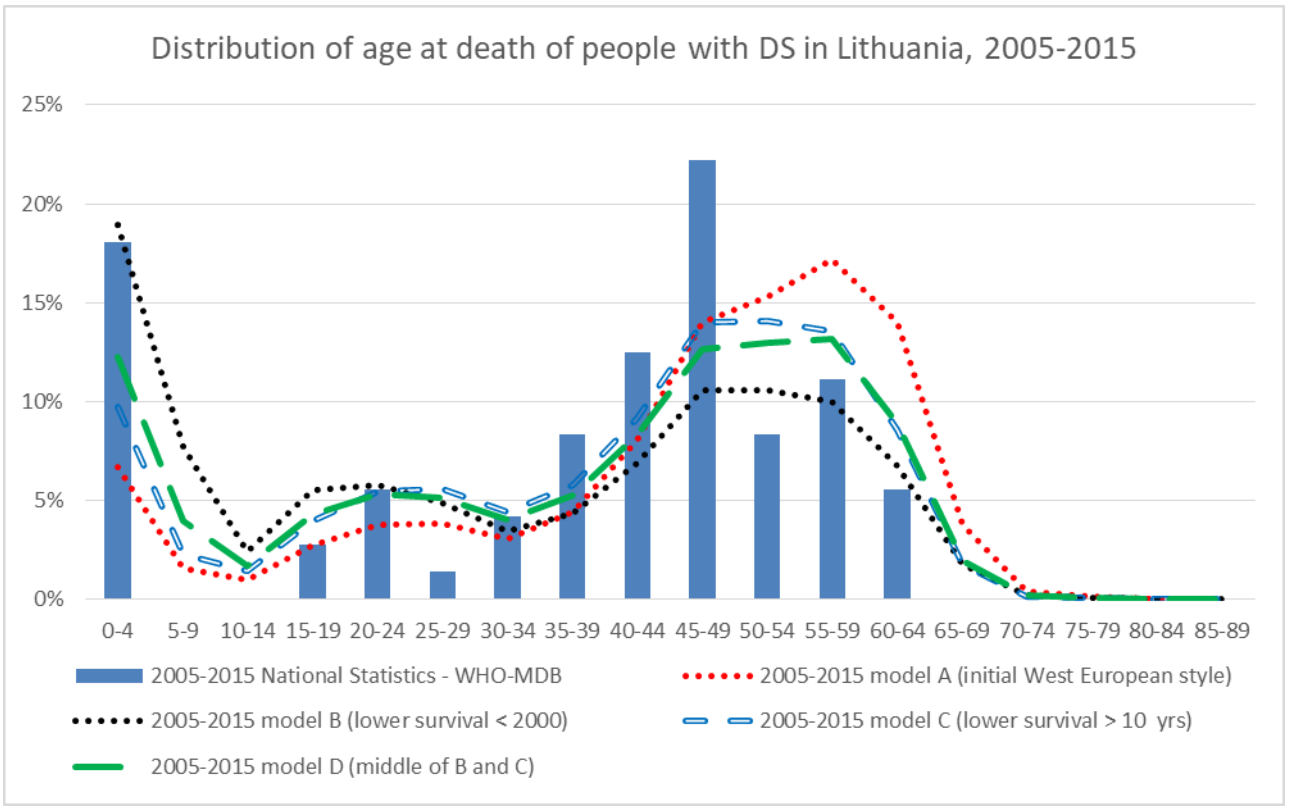
Lithuania

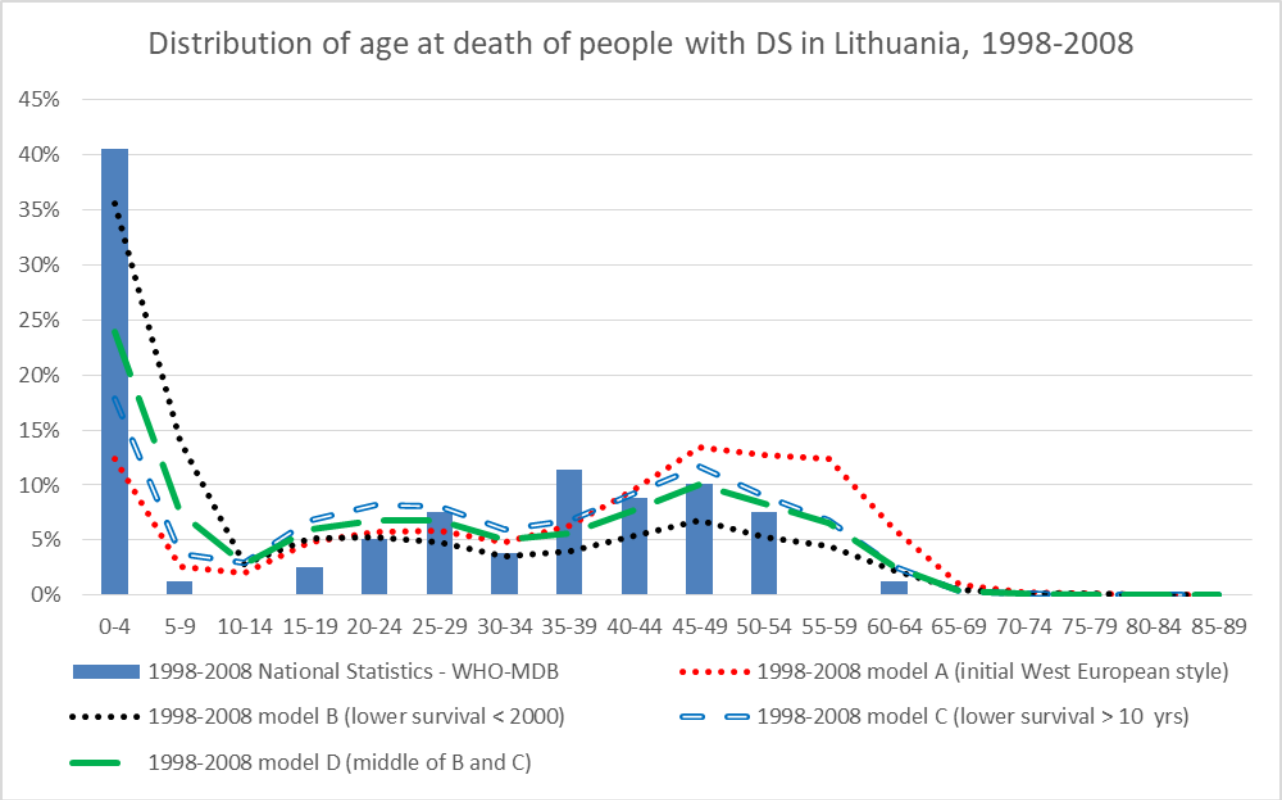
The WHO Mortality Database has data available for 1998–2017. The MDB contains data on 72 people with DS who died between 2005–2015, which is 19% of the number projected by Model A (West-European like survival) for the same period, 53% of the number projected by Model B, 27% of Model C, and 34% of Model D. For 1998–2008, this is 79 people, 30% of the projection of Model A, 65% of Model B, 43% of Model C, and 49% of Model D.

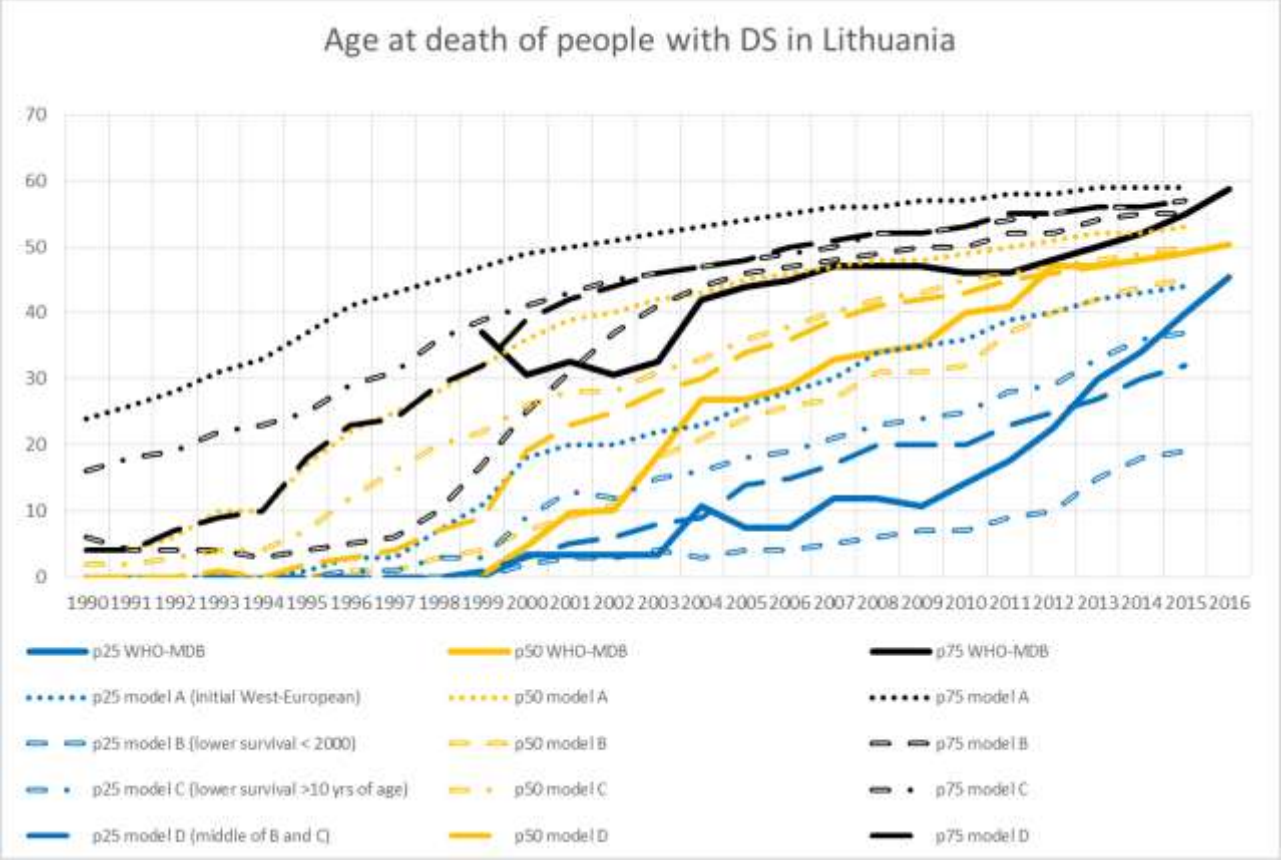
Looking at the graphs, the best fitting model seems to be Model C or D, of which we deem Model D to be more credible than model C.

For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and Model A is 0.7 ($p < 0.001$). Correlation of MDB with Model B is 0.8 ($p < 0.000$). With Model C, it is 0.84 ($p < 0.000$), and with Model D, it is 0.85 ($p < 0.000$). For 1998–2008, this is respectively 0.58 ($p < 0.011$) for Model A, 0.89 ($p < 0.000$) for Model B, 0.84 ($p < 0.000$) for Model C, and 0.84 ($p < 0.000$) for Model D. Model D has the best fit for 2005–2015; Model B has the best fit for 1998–2008, but differences between Model B and D are not large. Model A has the poorest fit.

In 2005–2015, the MDB has 47% of deceased people with DS being 45–70 years old. Model A has 64%, and model B has 40%. Model C has 52%, and Model D has 50%. In 1998–2008, the MDB value is 19%. Model A predicts 45%, and Model B predicts 19%. Model C predicts 30%, and Model D predicts 28%. In this regard, Model D seems to have the best fit for 2005–2015, and Model B has the best fit for 1998–2008.







Southern Europe

Albania
No data are available in the MDB.

Bosnia and Herzegovina
The WHO Mortality Database reports data on DS as cause of death for Bosnia and Herzegovina for 2011, 2014, and 2016. In total, 20 deaths are reported. These are such small numbers that looking at the age distribution would not be purposeful.

Croatia
The WHO Mortality Database has data available for 1995–2016. The MDB contains data on 192 people with DS who died between 2005–2015, which is 46% of the number projected by Model A (West-European like survival) for the same period, 120% of the number projected by Model B, 66% of Model C, and 81% of Model D. For 1995–2005, this is 190 people, 68% of the projection of Model A, 112% of Model B, 98% of Model C, and 101% of Model D. However, the cause of these high percentages, certainly for 1995–2005, seems to be a too low estimation of mortality in the 0–4 years age group in the models for recent years, as the MDB contains higher absolute numbers in this age range than the models predict. If we limit the comparison to the age group of 5 years and older, for the period 2005–2015, the MBD contains 38% of the number predicted by Model A, still 120% of Model B, 58% of Model C, and 73% of Model D. For 1995–2005, the situation changes into 30% of Model A, 90% of Model B, 49% of Model C, and 60% of Model D. The 120% for Model B for 2005–2015 and the 90% for 1995–2005 make this model less likely. However, Models C and D are very well possible, as the graph "Number of deceased people with DS in Croatia, 1995-2005" shows, whereas model A predicts too high number above 40 years of age.

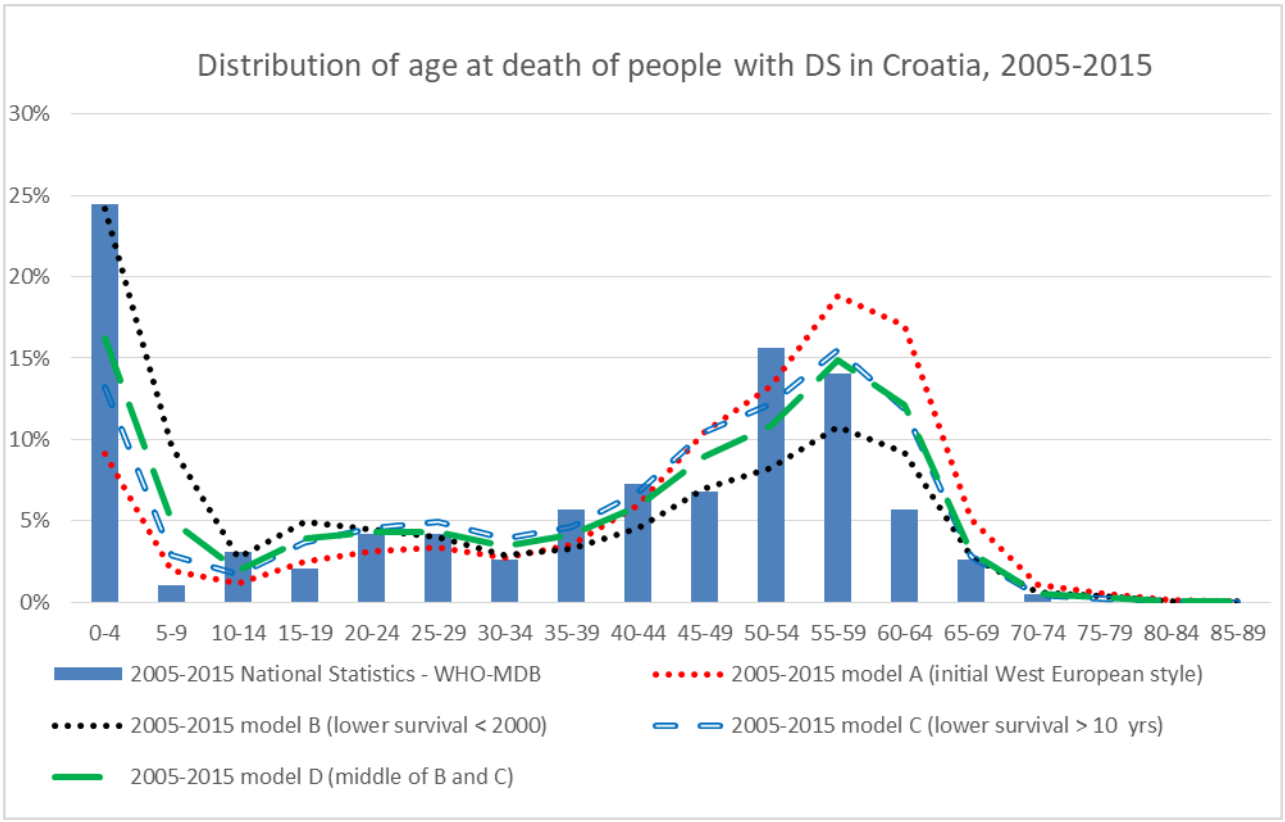
However, Model B seems to have a better fit in regards to the 1-year mortality of people with DS in recent years. To illustrate this, we have added 2 extra graphs: "Number of deceased people with DS up to 1 year of age in Croatia" and "1-year mortality in people with DS in Croatia." These graphs show that 1-year mortality has been underestimated in all models for the period 1995–2012. From 2002 onwards, all models have the same prediction, which is lower than the MDB for the period 2002–2012 and similar for 2012–2015. For 1995–2005, Model B predicts the highest 1-year mortality of the 4 models, but even this is lower than the estimate of the MDB. As probably not every deceased child with DS is reported as having DS as primary cause of death, the real mortality may even have been higher than that of the MDB. However, the estimation of the 1-year mortality rates can be influenced by the estimation of the number of LBs with DS. But, even if we assume there were no elective terminations of children with DS during 1995–2015, 1-year mortality estimates of the MBD are still clearly higher than estimates based on the models. The conclusion is that Model B has the strongest fit with the MDB data in regards to 1-year mortality rates in the period 1995–2002, though probably this is still is an under-estimation. If mortality after 1 year of age, including mortality in adulthood is also less favorable than modeled in recent years, Model B could be a correct approximation of 1-year mortality in the past, as a less favorable survival nowadays would explain why the reported numbers in the MDB above 5 years of age are higher than the numbers predicted by Model B. At the other hand, it is also possible that Model B overestimates 1-year mortality before 1995.

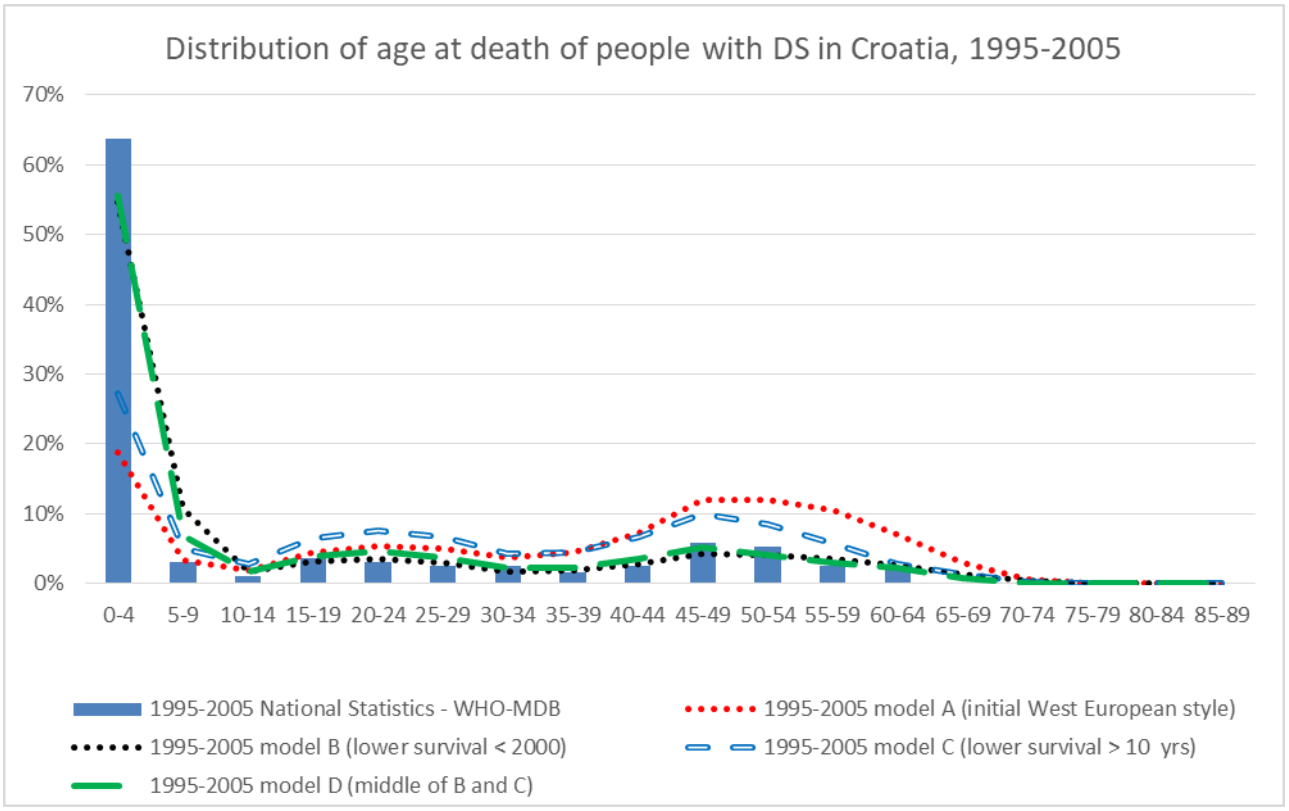
Looking at the graphs on age distribution of deceased people with DS, the best fitting model seems to be Models C or D, of which we deem Model D to be more credible than model C.

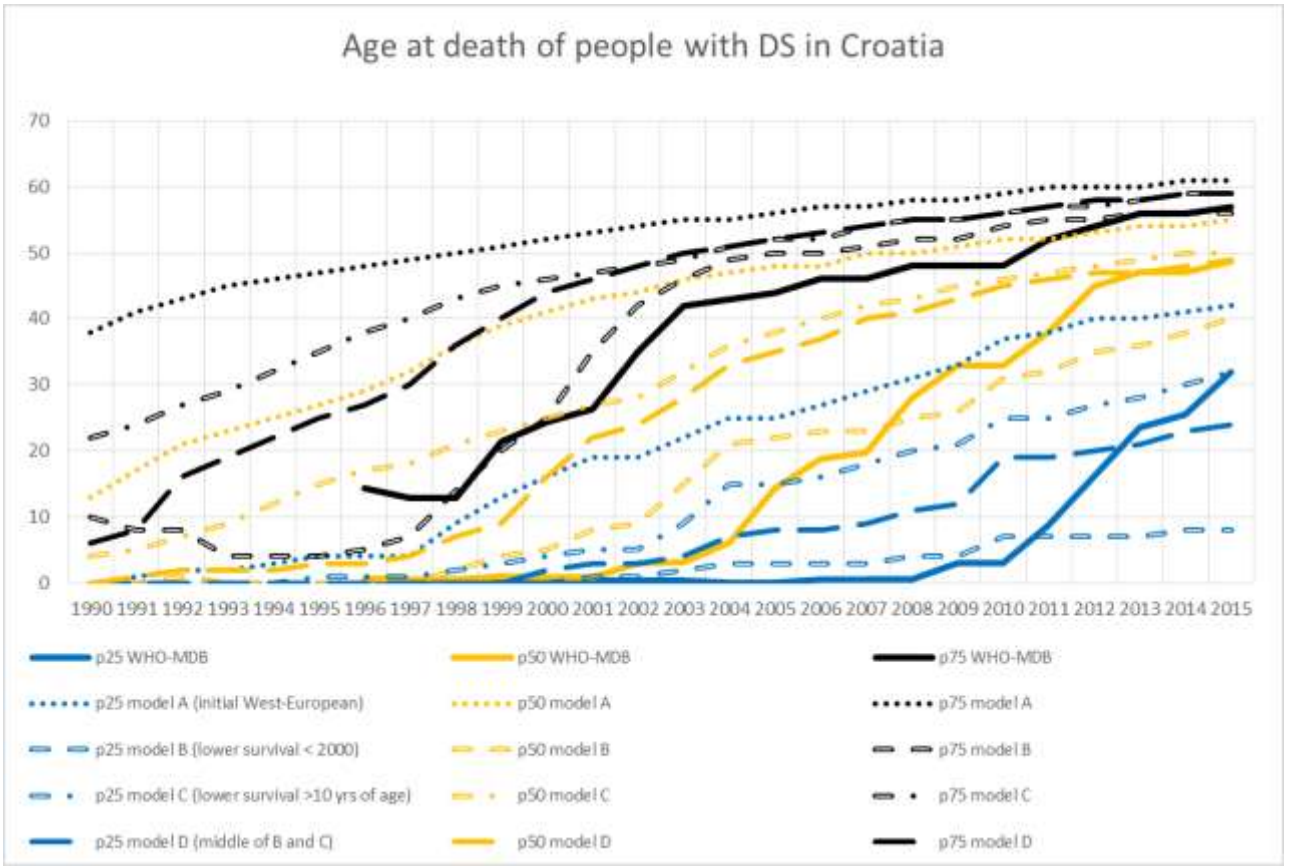
For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.68 ($p < 0.002$). Correlation of MDB with Model B is 0.87 ($p < 0.000$). With Model C, it is 0.85 ($p<0.000$), and with Model D, it is 0.89 ($p < 0.000$). For 1995–2005, this is

respectively 0.73 (p <0.001) for model A, 0.99 (p < 0.000) for Model B, 0.92 (p <0.000) for Model C, and 0.98 (p <0.000) for Model D. Model D, has the best fit for 2005–2015,and Model B has the best fit for 1995–2005, but differences between Model B and D are not large. Model A has the poorest fit.

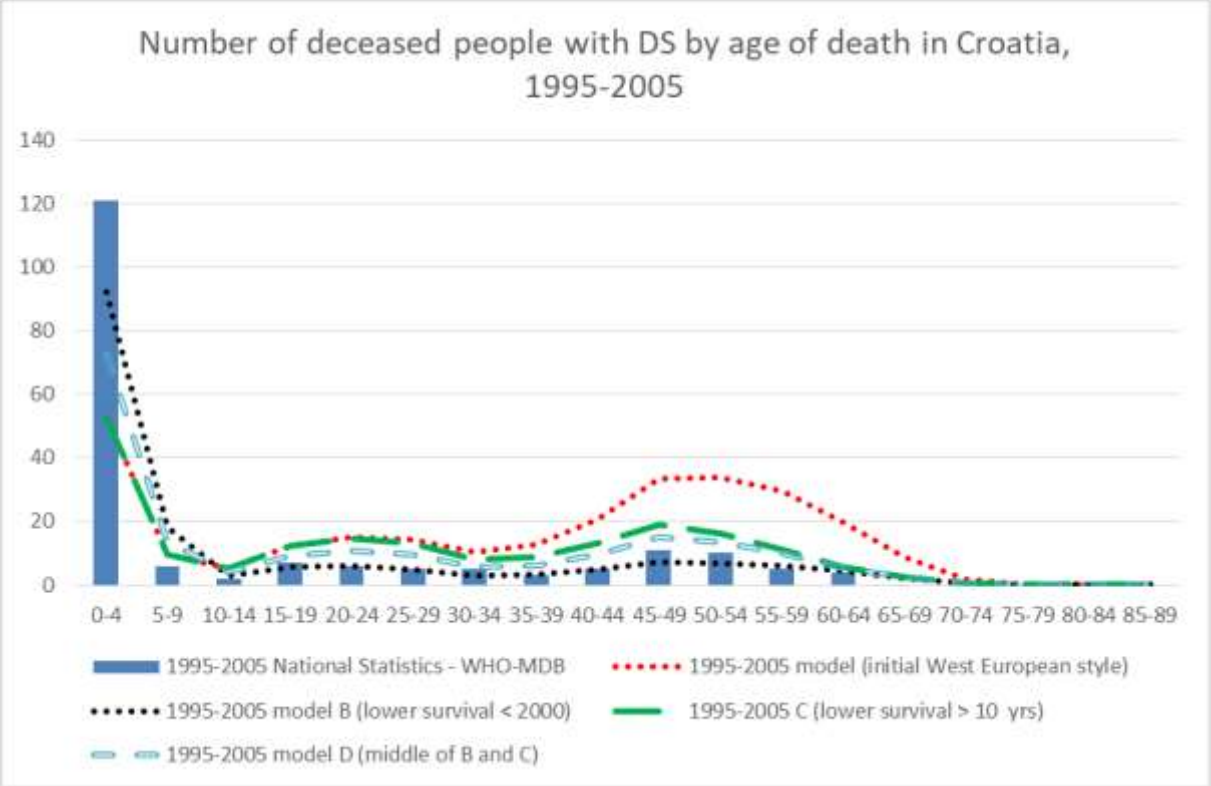
In 2005–2015, the MDB has 45% of deceased people with DS in the 45–70 year age group. Model A has 65%, and Model B has 38%. Model C has 53%, and Model D has 50%. In 1995–2005, the MDB value is 16%. Model A predicts 45%, and Model B predicts 16%. Model C predicts 28%, and Model D predicts 25%. In this regard, Model D seems to have the best fit for2005–2015, and Model B has the best fit for 1995–2005.

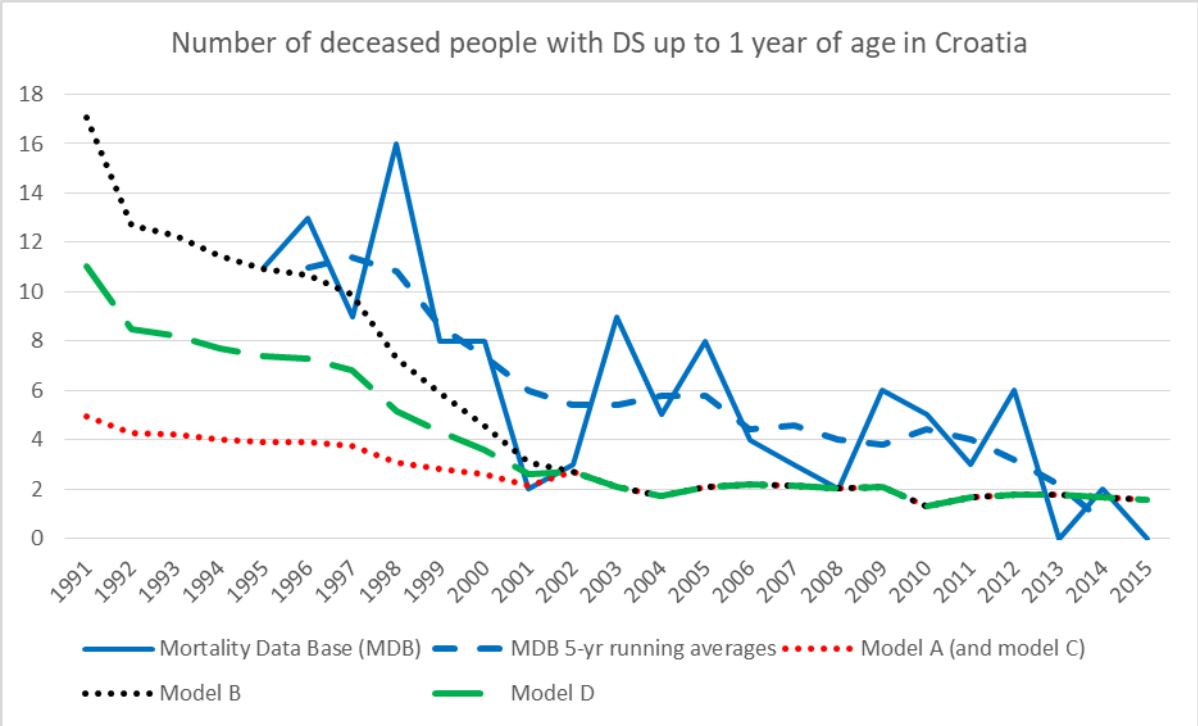


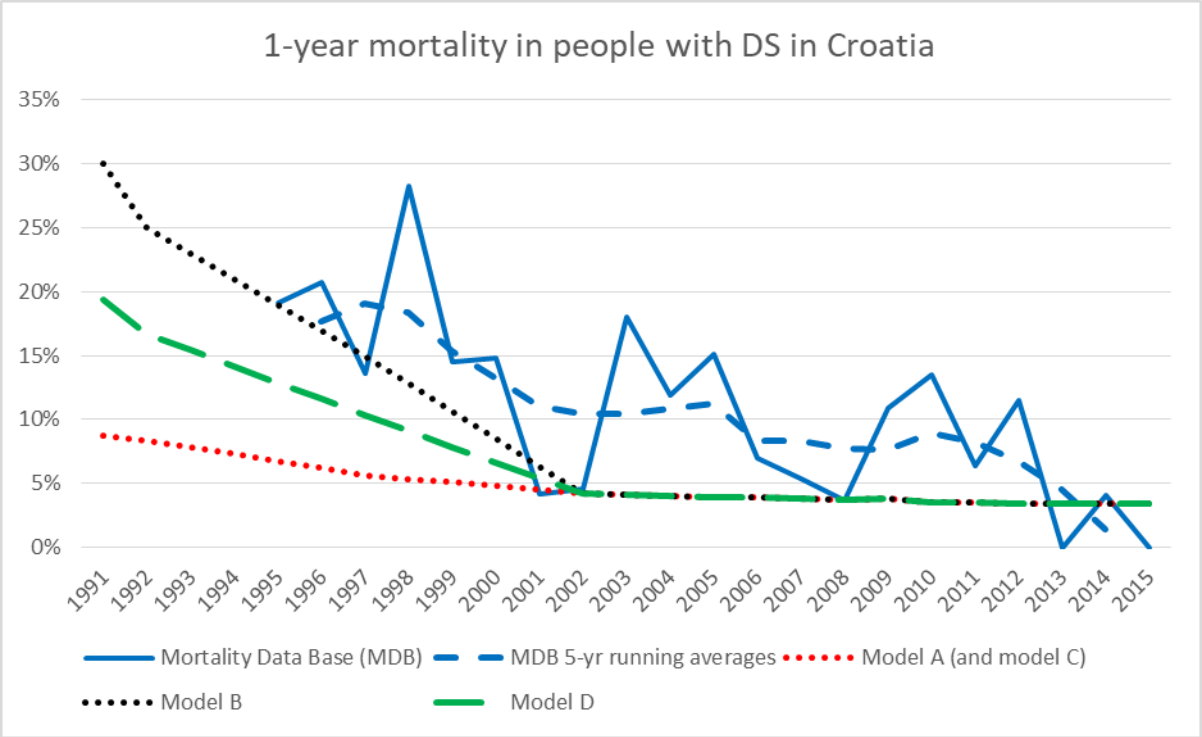

Distribution of age at death of people with DS in Croatia, 1995-2005
70%
60%
50%
40%
30%
20%
10%
0%
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
1995-2005 National Statistics - WHO-MDB
1995-2005 model A (initial West European style)
1995-2005 model B (lower survival < 2000)
1995-2005 model C (lower survival > 10 yrs)
1995-2005 model D (middle of B and C)


Age at death of people with DS in Croatia
70
60
50
40
30
20
10
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model A (initial West-European)
p50 model A
p75 model A
p25 model B (lower survival < 2000)
p50 model B
p75 model B
p25 model C (lower survival >10 yrs of age)
p50 model C
p75 model C
p25 model D (middle of B and C)
p50 model D
p75 model D

In the graph below, absolute numbers of deceased people with DS are presented, instead of the distribution over age groups as percentages of the total number.







Montenegro

The WHO Mortality Database reports data on DS as cause of death for Montenegro for 2002–2007. In total 18 deaths are reported. This is such a small number that looking at the age distribution would not be purposeful.

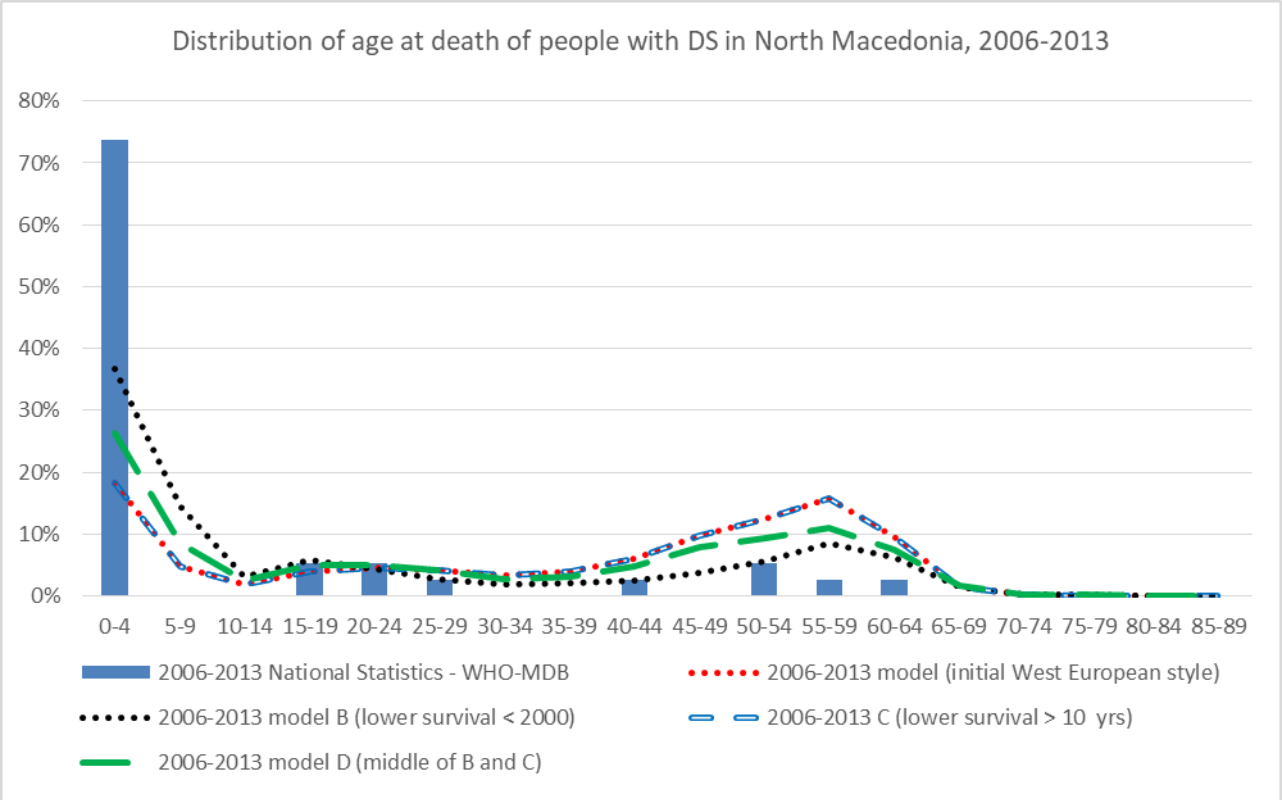
North Macedonia

The WHO Mortality Database has data available for 2006–2013. The MDB contains data on 38 people with DS who died, which is 47% of the number projected by model A (West-European like survival) for the same period, 96% of the number projected by Model B, 47% of Model C, and 70% of Model D. However, the cause of these relatively high percentages (especially for Model B) seems to be too low of an estimation for mortality in the 0–4 year age group in the models for recent years, as the MDB contains higher absolute numbers in this age range than the models predict. The assumption that in recent years North Macedonia will have been similar to former West bloc countries in regards to the 1-year mortality for children with DS appears to be incorrect. For 2006–2013, the MDB registered 25 deaths of children with DS up to 1 year of age (corresponding to a 15% 1-year mortality rate), whereas the models predict only 9 deaths in this age range (corresponding to a 5% 1-year mortality rate).

Looking at the graph on age distribution of deceased people with DS, the best fitting model for 2006–2013 seems to be Model B, followed by Model D.

For 2006–2013, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.62 ($p < 0.006$). Correlation of MDB with Model B is 0.92 ($p < 0.000$). With Model C, it is 0.62 ($p < 0.006$), and with Model D, it is 0.87 ($p < 0.000$). Model B has the best fit, followed by model D.

In 2006–2013, the MDB has 11% of deceased persons with DS in 45–70 year age group. Model A has 49%, and Model B has 26%. Model C has 49%, and Model D has 36%. Model B seems to have the best fit.



As the range of years is relatively short (only 8 years) with very limited numbers by year, it would not be purposeful to draw the graph with the development of 25th, 50th, and 75th percentiles of age at death.

Serbia

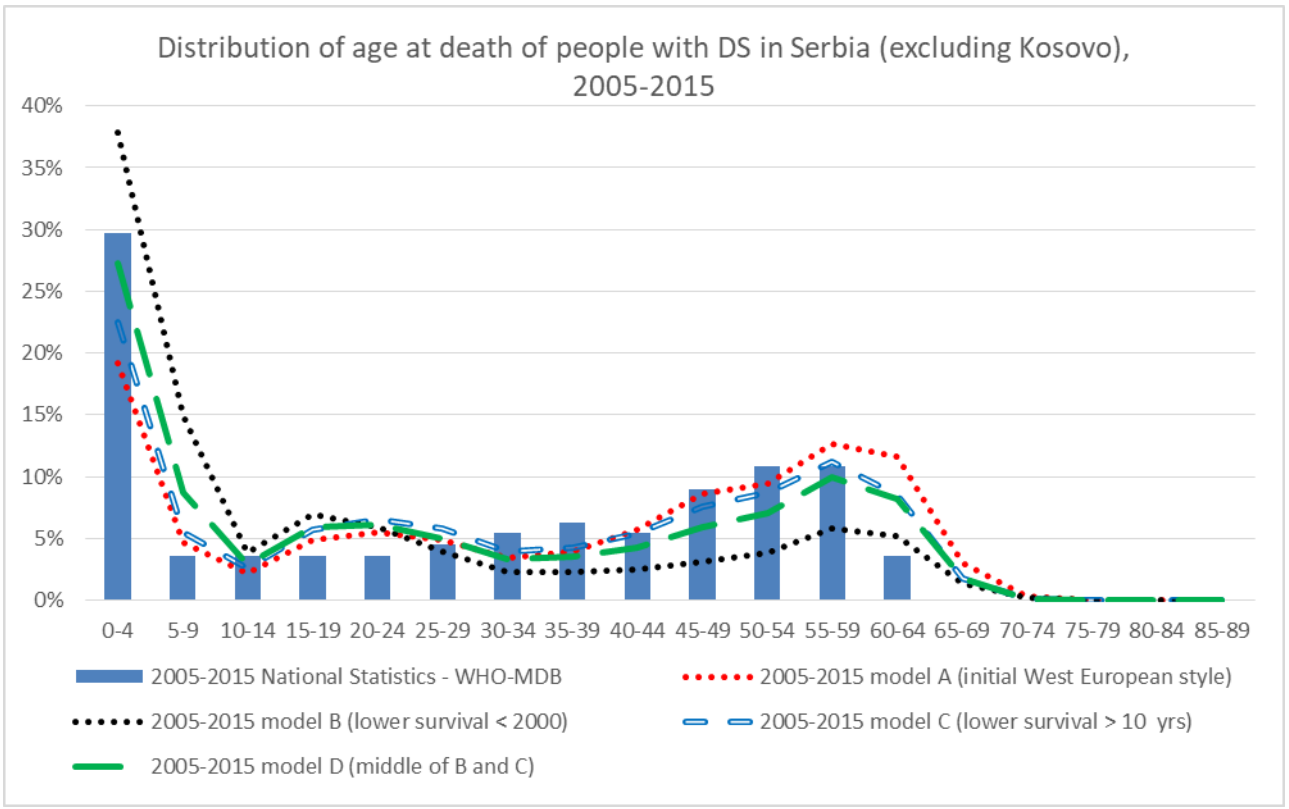
The WHO Mortality Database has data available for 1998–2015. As these are for Serbia without Kosovo, for comparison, we have used the numbers for Serbia without Kosovo from our models, too. The MDB contains data on 111 people with DS who died between 2005–2015, which is 23% of the number projected by model A (West-European like survival) for the same period, 45% of the number projected by Model B, 27% of Model C, and 33% of Model D. For 1998–2008, this is 119 people, 47% of the projection of model A, 66% of Model B, 54% of Model C, and 58% of Model D.

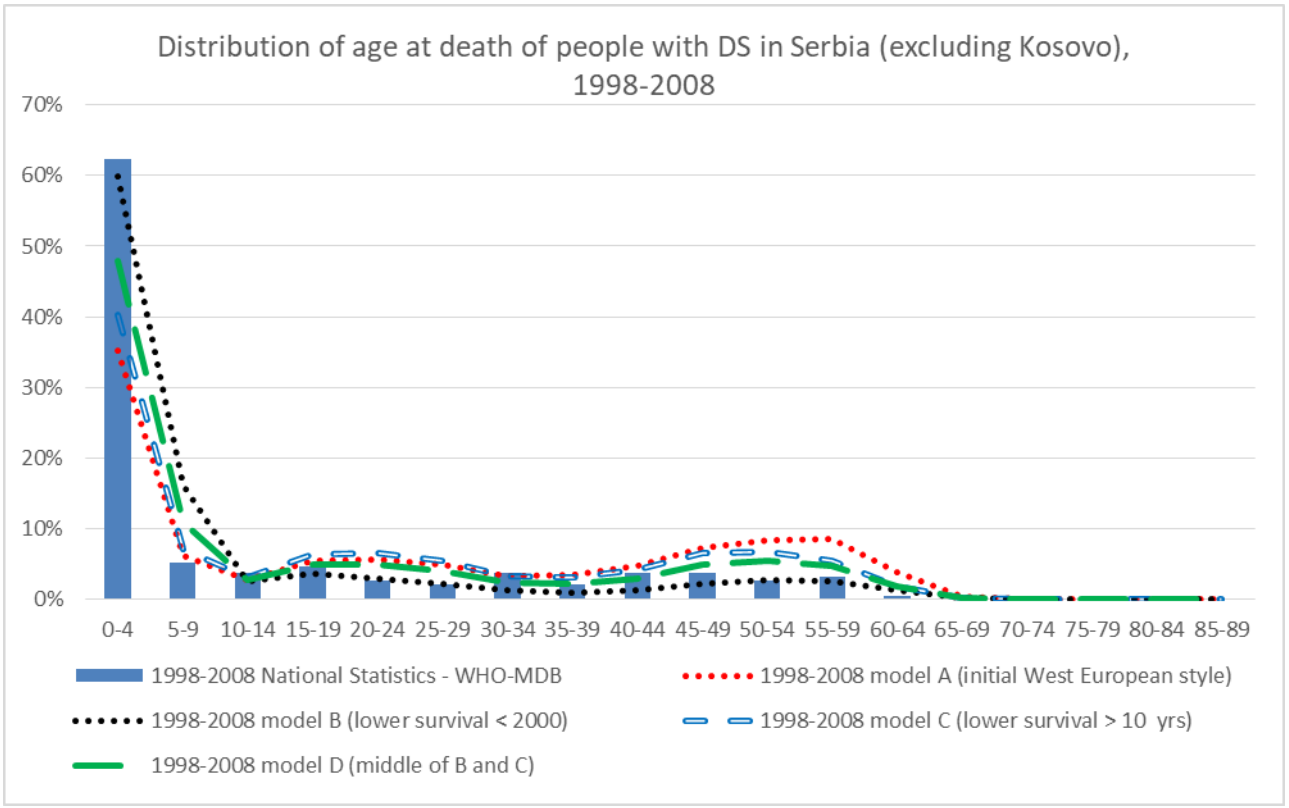
Looking at the graphs on age distribution of deceased people with DS, the best fitting model seems to be Models C or D, of which we deem Model D to be more credible than model C. Model A appears to have a rather good fit for the period 2005–2015, but less so for 1998–2008. Model B seems to have a rather poor fit, especially for 2005–2015.

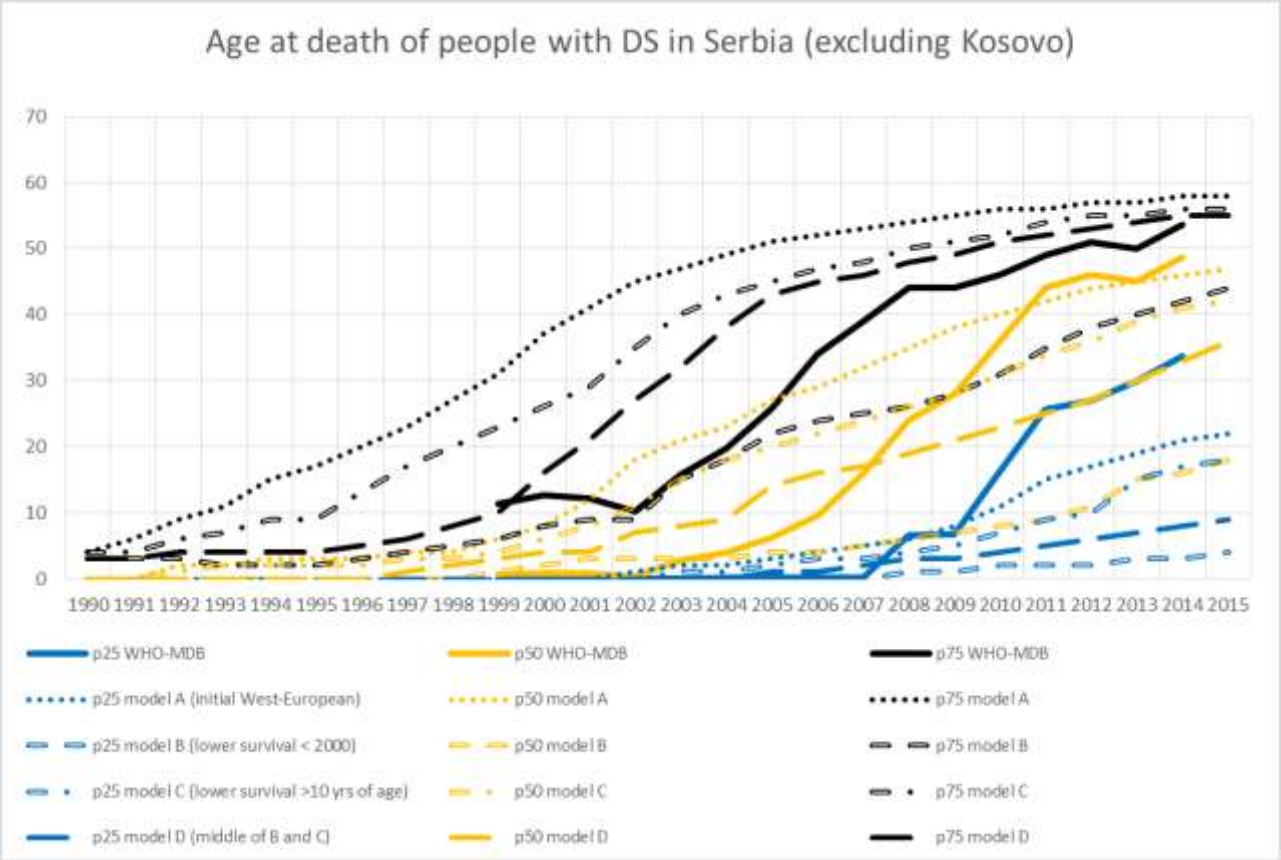
For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.88 ($p < 0.000$). Correlation of MDB with Model B is 0.86 ($p < 0.000$). With Model C, it is 0.95 ($p < 0.000$), and with Model D, it is 0.93 ($p < 0.000$). For 1998–2008, this is respectively 0.96 ($p < 0.001$) for model A, 0.98 ($p < 0.000$) for Model B, 0.98 ($p < 0.000$) for Model C, and 0.99 ($p < 0.000$) for Model D. Model C (followed by Model D) has the best fit for 2005–2015, and Model D has the best fit for 1998–2008, but differences between models are small for 1998–2008.

In 2005–2015, the MDB has 34% of deceased people with DS in the 45–70 year age group. Model A has 45%, and Model B has 19%. Model C has 38%, and Model D has 33%. In 1998–2008, the MDB value is 10%. Model A predicts 28%, and Model B predicts 9%. Model C predicts 21%, and Model D

predicts 17%. In this regard, Model D (and C) seems to have the best fit for 2005–2015, and Model B has the best fit for 1998–2008.







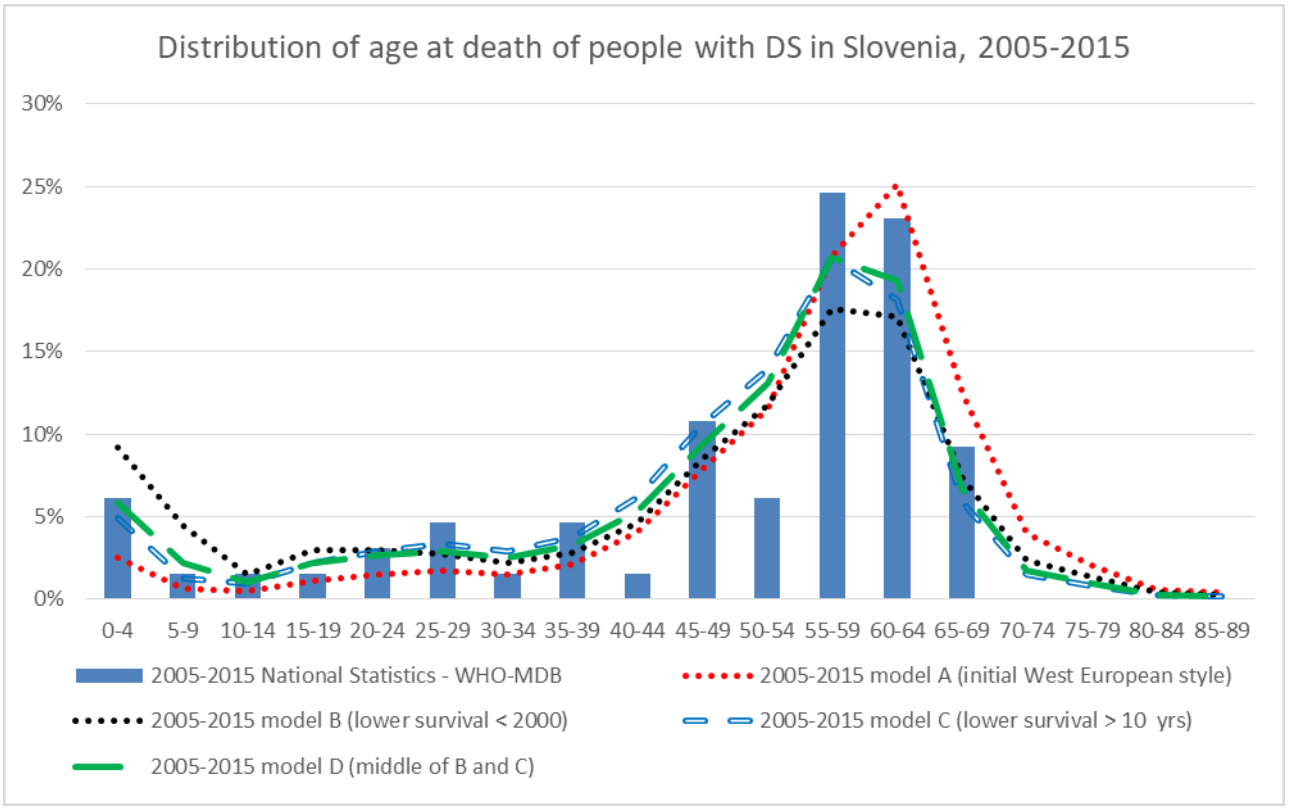
Slovenia

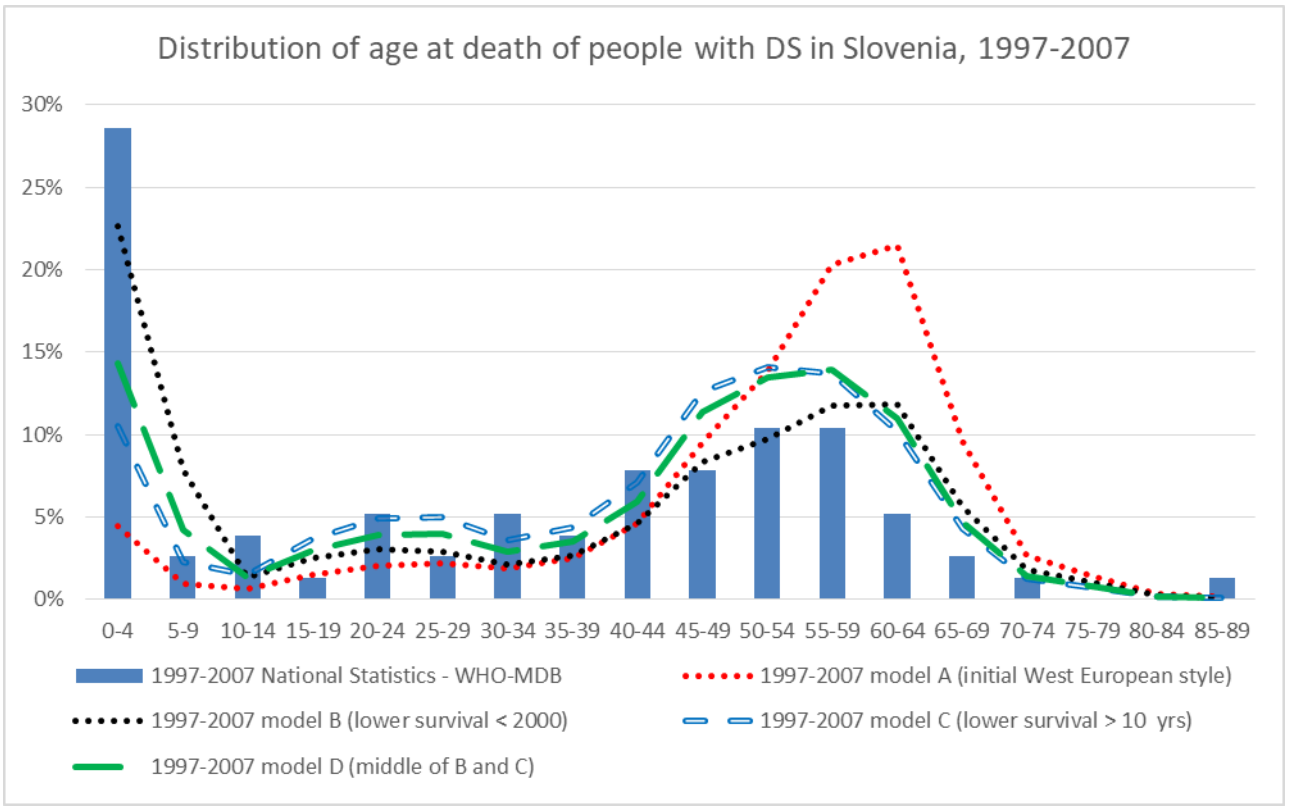
The WHO Mortality Database has data available for 1997–2015. The MDB contains data on 65 people with DS who died between 2005–2015, which is 18% of the number projected by model A (West-European like survival) for the same period, 65% of the number projected by Model B, 35% of Model C, and 42% of Model D. For 1998–2008, this is 77 people, 23% of the projection of model A, 81% of Model B, 56% of Model C, and 61% of Model D.

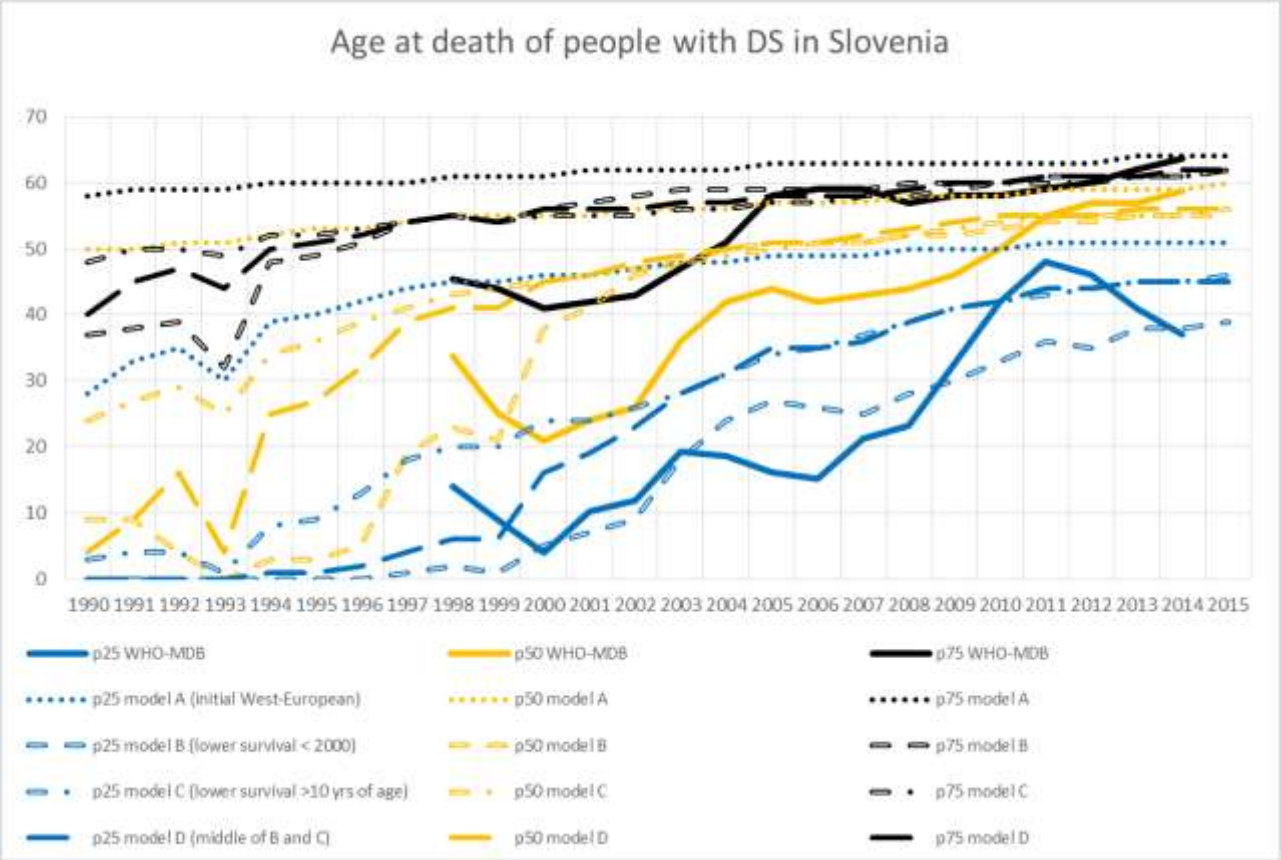
Looking at the graphs on age distribution of deceased people with DS, the best fitting model for 2005–2015 seems to be Models C or D, of which we deem Model D to be more credible than Model C. Model A appears to have a rather good fit for the period 2005–2015 but not a good fit for 1997–2007. Model B seems to have a rather poor fit for 2005–2015 but seems to have a good fit for 1997–2007.

For 2005–2015, in regards to the age distribution of deceased people with DS, the correlation between MDB and model A is 0.93 ($p < 0.000$). Correlation of MDB with Model B is 0.93 ($p < 0.000$). With Model C, it is 0.92 ($p < 0.000$), and with Model D, it is 0.94 ($p < 0.000$). Model D has the best fit, but differences between models are small in this regard. For 1997–2007, this is respectively 0.29 ($p < 0.24$) for model A, 0.89 ($p < 0.000$) for Model B, 0.65 ($p < 0.000$) for Model C, and 0.77 ($p<0.000$) for Model D. For this period, Model B has the best fit, followed by Model D.

In 2005–2015, the MDB has 74% of deceased persons with DS in the 45–70 year age group. Model A has 78%, and Model B has 62%. Model C has 69%, and Model D has 69%. In 1997–2007, the MDB value is 36%. Model A predicts 75%, and Model B predicts 47%. Model C predicts 55%, and Model D predicts 54%. In this regard, Model D (and C) seems to have the best fit for 2005–2015, and Model B has the best fit for 1998–2008.


Distribution of age at death of people with DS in Slovenia, 2005-2015
30%
25%
20%
15%
10%
5%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
2005-2015 National Statistics - WHO-MDB
2005-2015 model A (initial West European style)
2005-2015 model B (lower survival < 2000)
2005-2015 model C (lower survival > 10 yrs)
2005-2015 model D (middle of B and C)


Distribution of age at death of people with DS in Slovenia, 1997-2007
30%
25%
20%
15%
10%
5%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
1997-2007 National Statistics - WHO-MDB
1997-2007 model A (initial West European style)
1997-2007 model B (lower survival < 2000)
1997-2007 model C (lower survival > 10 yrs)
1997-2007 model D (middle of B and C)



Eastern Europe

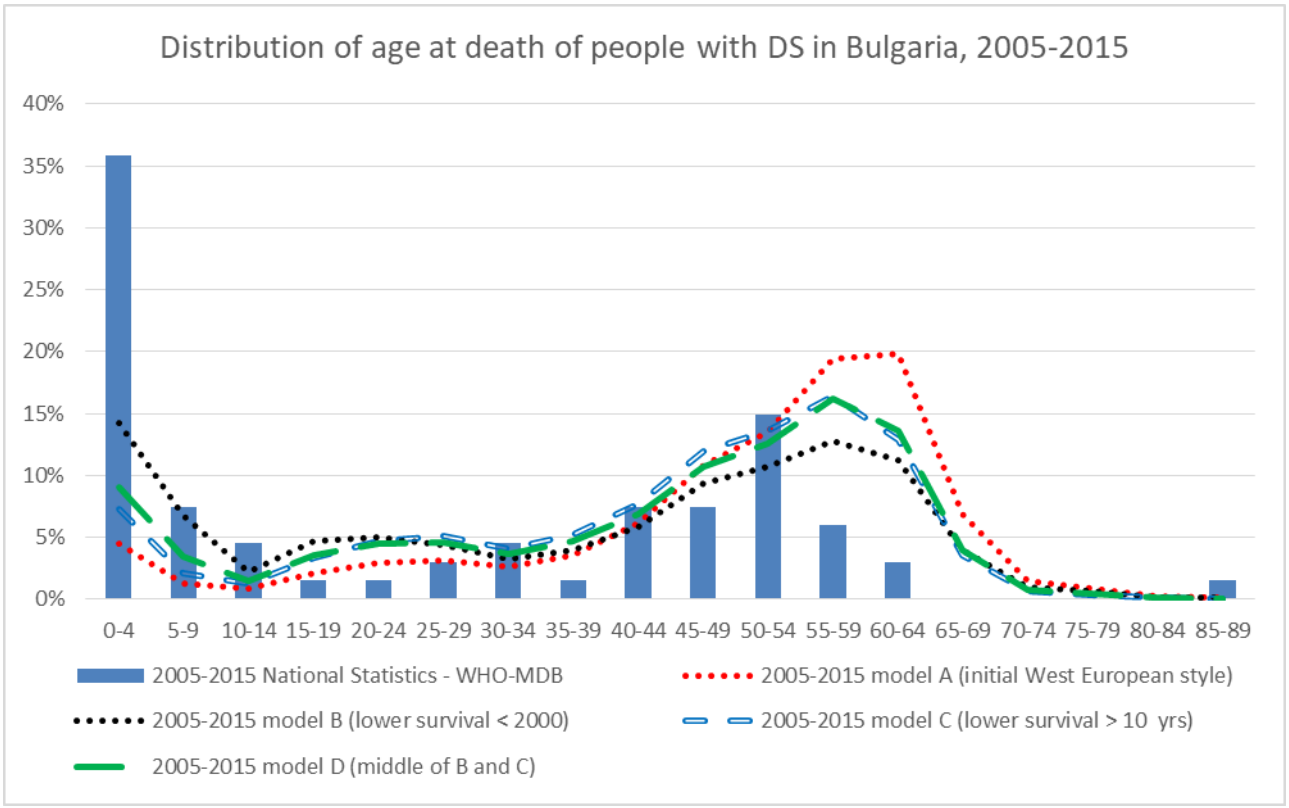
Belarus
No data are available in the MDB.

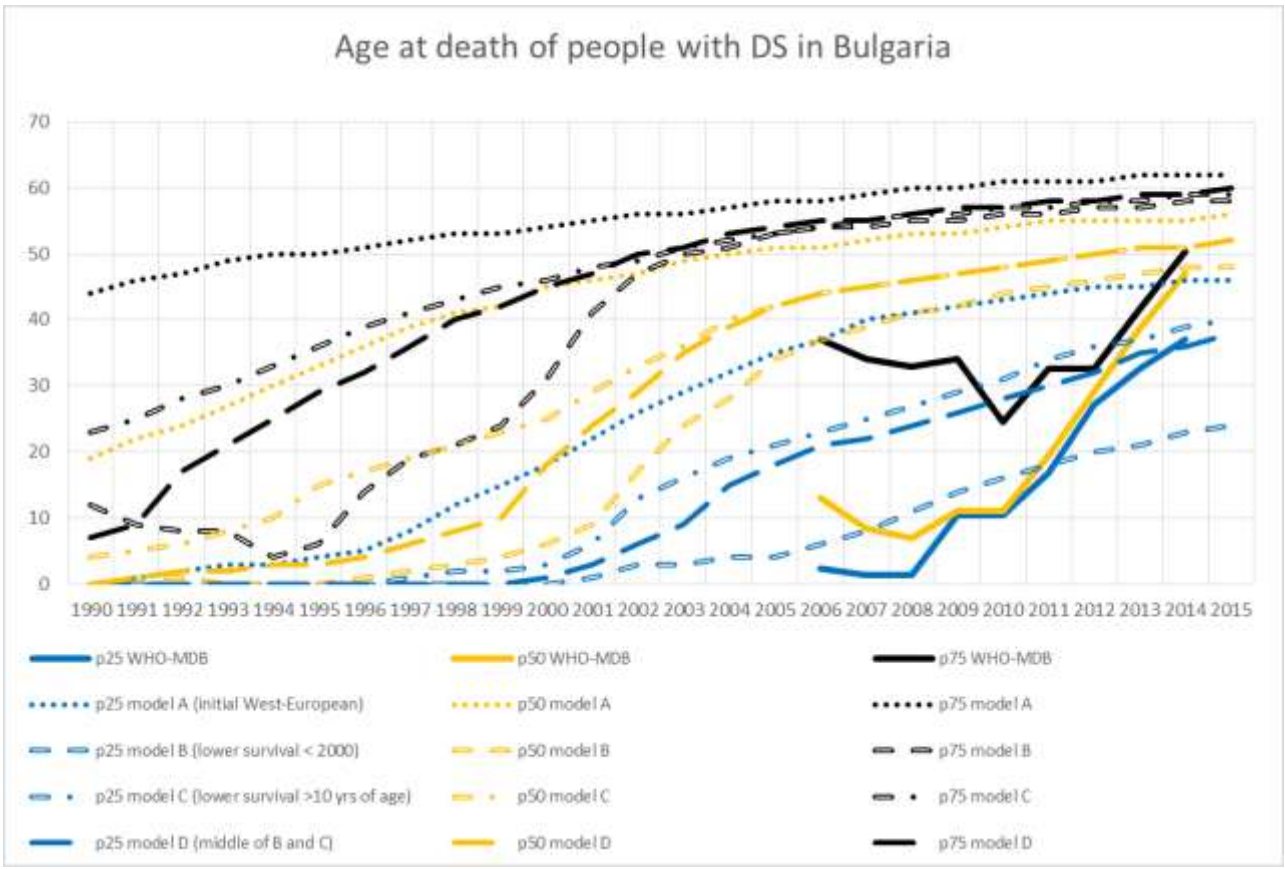
Bulgaria
The WHO Mortality Database has data available for 2005–2015. The MDB contains data on 67 people with DS who died, which is 9% of the number projected by model A (West-European like survival) for the same period, 30% of the number projected by Model B, 15% of Model C, and 19% of Model D.

Looking at the graph on age distribution of deceased people with DS, the best fitting model for 2005–2015 seems to be Model D or Model B.

For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.17 ($p < 0.49$). Correlation of MDB with Model B is 0.7 ($p < 0.001$). With Model C, it is 0.36 ($p < 0.14$), and with Model D, it is 0.43 ($p < 0.074$). Model B has the best fit.

In 2005–2015, the MDB has 31% of deceased people with DS in the 45–70 year age group. Model A has 70%, and Model B has 48%. Model C has 58%, and Model D has 57%. Model B seems to have the best fit.


Distribution of age at death of people with DS in Bulgaria, 2005-2015
40%
35%
30%
25%
20%
15%
10%
5%
0%
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
2005-2015 National Statistics - WHO-MDB
2005-2015 model A (initial West European style)
2005-2015 model B (lower survival < 2000)
2005-2015 model C (lower survival > 10 yrs)
2005-2015 model D (middle of B and C)


Age at death of people with DS in Bulgaria
70
60
50
40
30
20
10
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model A (initial West-European)
p50 model A
p75 model A
p25 model B (lower survival < 2000)
p50 model B
p75 model B
p25 model C (lower survival >10 yrs of age)
p50 model C
p75 model C
p25 model D (middle of B and C)
p50 model D
p75 model D

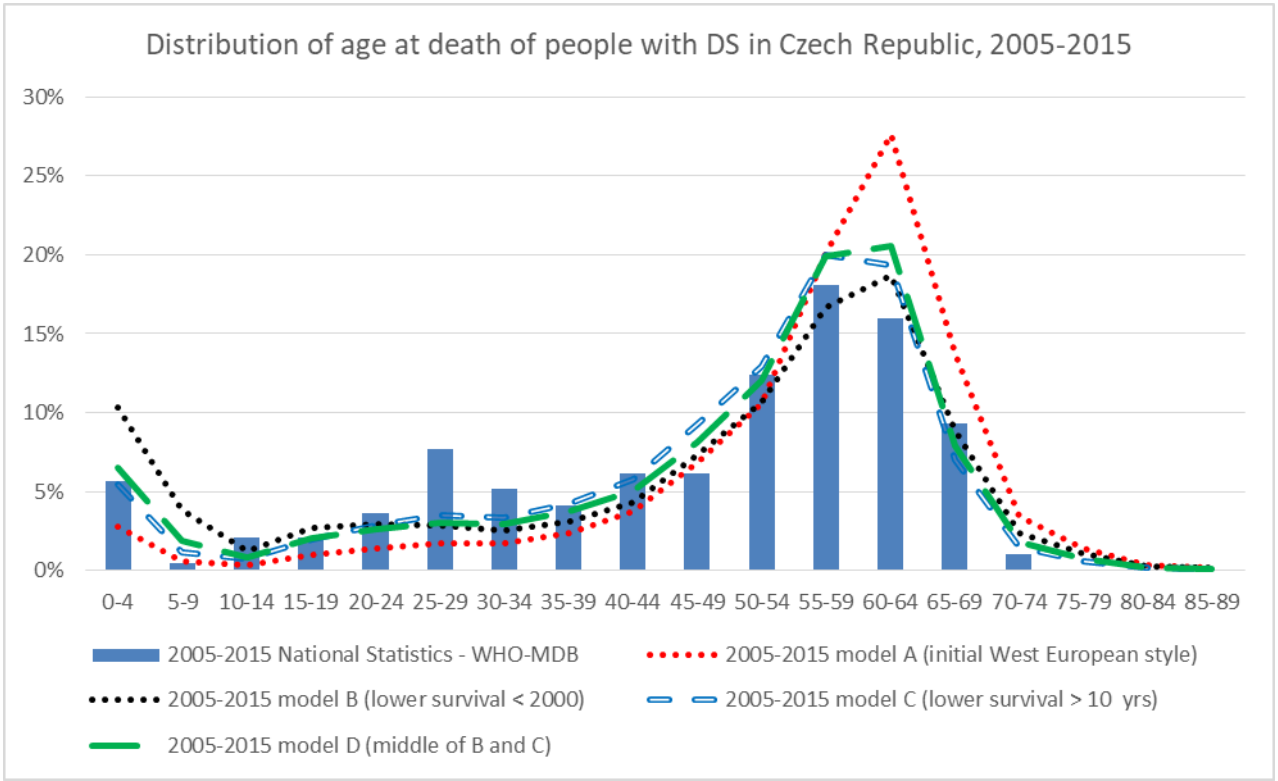
Czech Republic

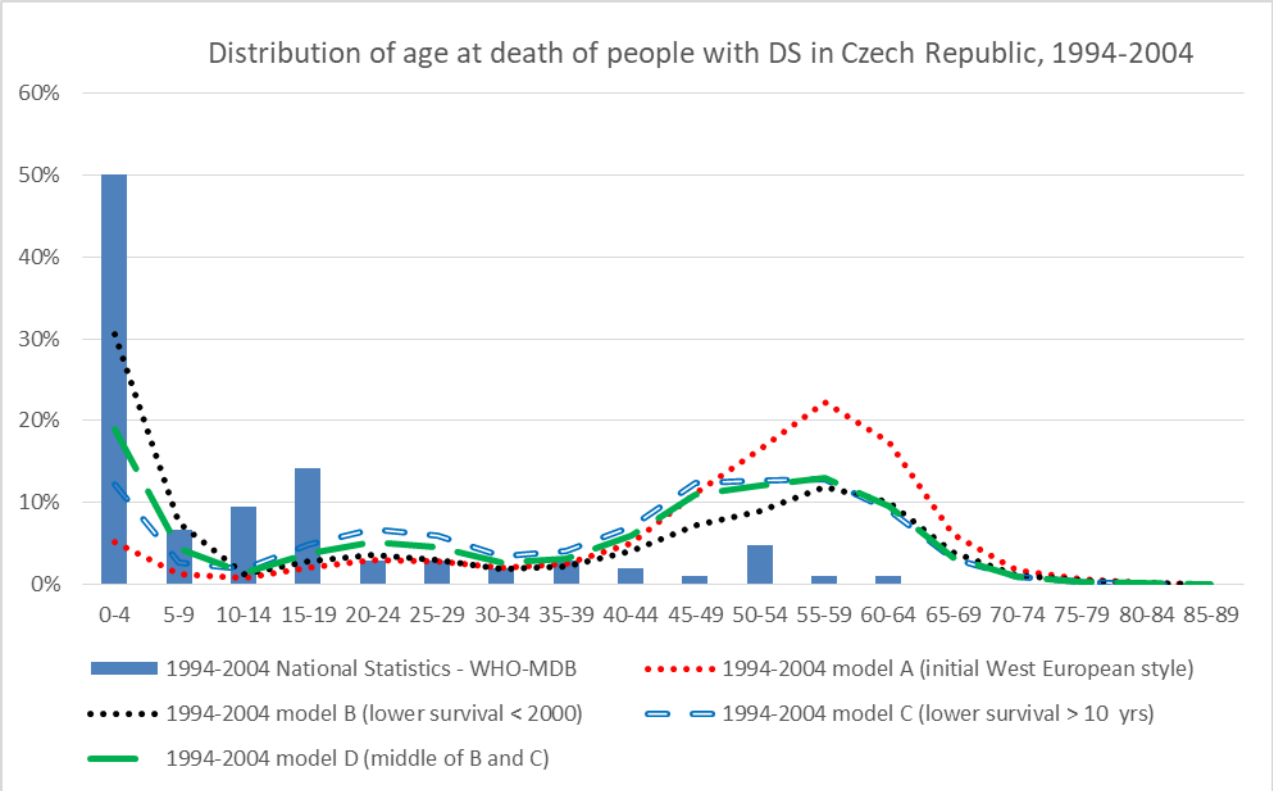
The WHO Mortality Database has data available for 1994–2016. The MDB contains data on 194 people with DS who died between 2005–2015, which is 15% of the number projected by model A (West-European like survival) for the same period, 54% of the number projected by Model B, 29% of Model C, and 35% of Model D. For 1994–2004, this is 106 people, 10% of the projection of model A, 31% of Model B, 24% of Model C, and 25% of Model D.

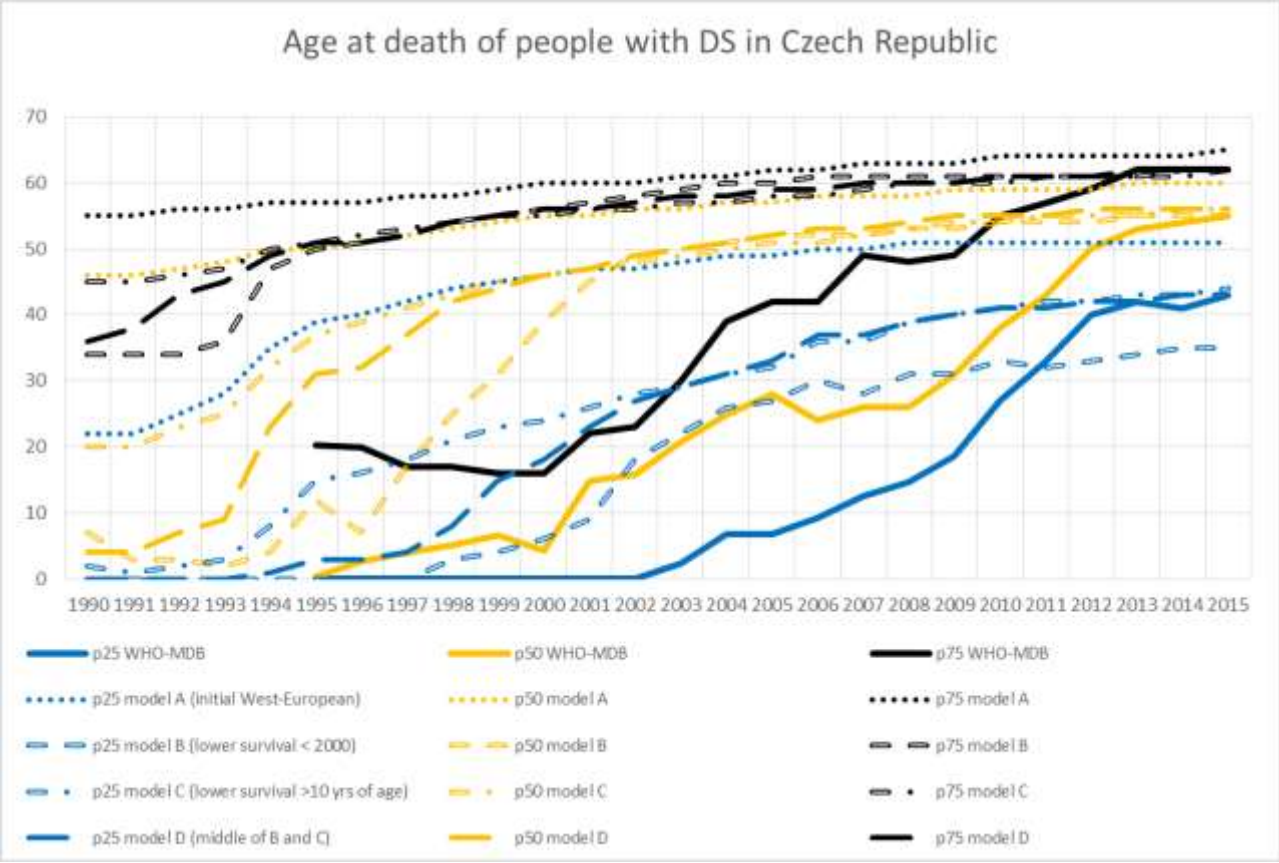
Looking at the graphs on age distribution of deceased people with DS, the best fitting model for 2005–2015 seems to be Models C or D, of which we deem Model D to be more credible than model C. Model A has a poor fit for the period 2005–2015 and for 1994–2004.

For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.89 ($p < 0.000$). Correlation of MDB with Model B is 0.92 ($p < 0.000$). With Model C, it is 0.96 ($p < 0.000$), and Model D it is 0.95 ($p < 0.000$). Model C and Model D have the best fit. For 1994–2004, this is respectively -0.07 ($p < 0.79$) for model A, 0.82 ($p < 0.000$) for Model B, 0.35 ($p < 0.15$) for Model C, and 0.60 ($p < 0.009$) for Model D. For this period, model B has the best fit, followed by Model D.

In 2005–2015, the MDB has 63% of deceased people with DS in the 45–70 year age group. Model A has 79%, and Model B has 62%. Model C has 68%, and Model D has 68%. In 1994–2004, the MDB value is 8%. Model A predicts 73%, and Model B predicts 42%. Model C predicts 50%, and Model D predicts 49%. In this regard, Model B, followed by model D (and C) seems to have the best fit for 2005–2015, and Model B has the best fit for 1994–2004, though the discrepancy between this model and MDB is large.







Hungary

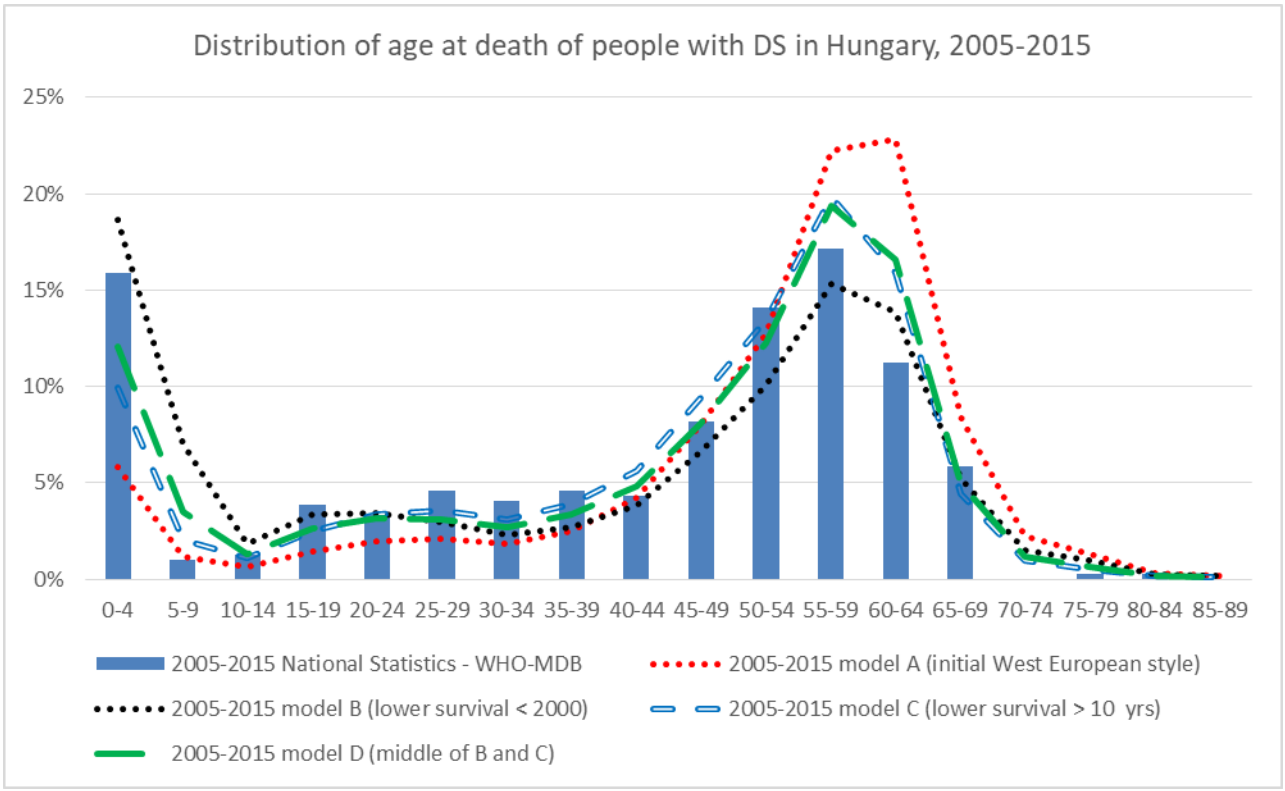
The WHO Mortality Database has data available for 1996–2017. The MDB contains data on 391 people with DS who died between 2005–2015, which is 39% of the number projected by model A (West-European like survival) for the same period, 125% of the number projected by Model B, 67% of

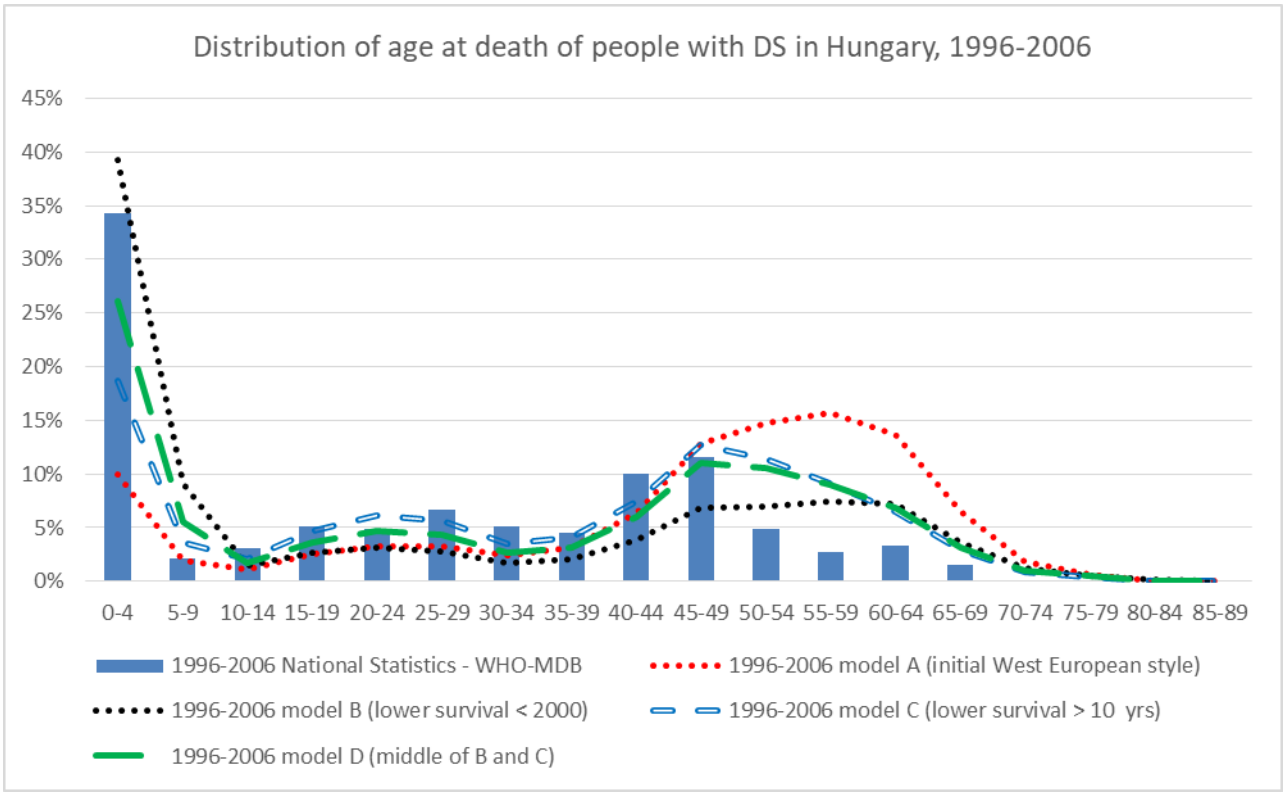
Model C, and 81% of Model D. For 1996–2006, this is 329 people, 45% of the projection of model A, 101% of model B, 85% of Model C, and 91% of Model D. The high percentages for Model B make this model unlikely. The cause of these high percentages cannot be explained by an under-estimation of mortality in the 0–4 year age group in the models for recent years. If we limit the comparison to the age group to 5 years and older, for both periods, the MBD still contains more deaths than Model B predicts. However, 1-year mortality in recent years appears to be an underestimation in all the models, as can be seen in the extra graph: "1-year mortality in people with DS in Hungary."

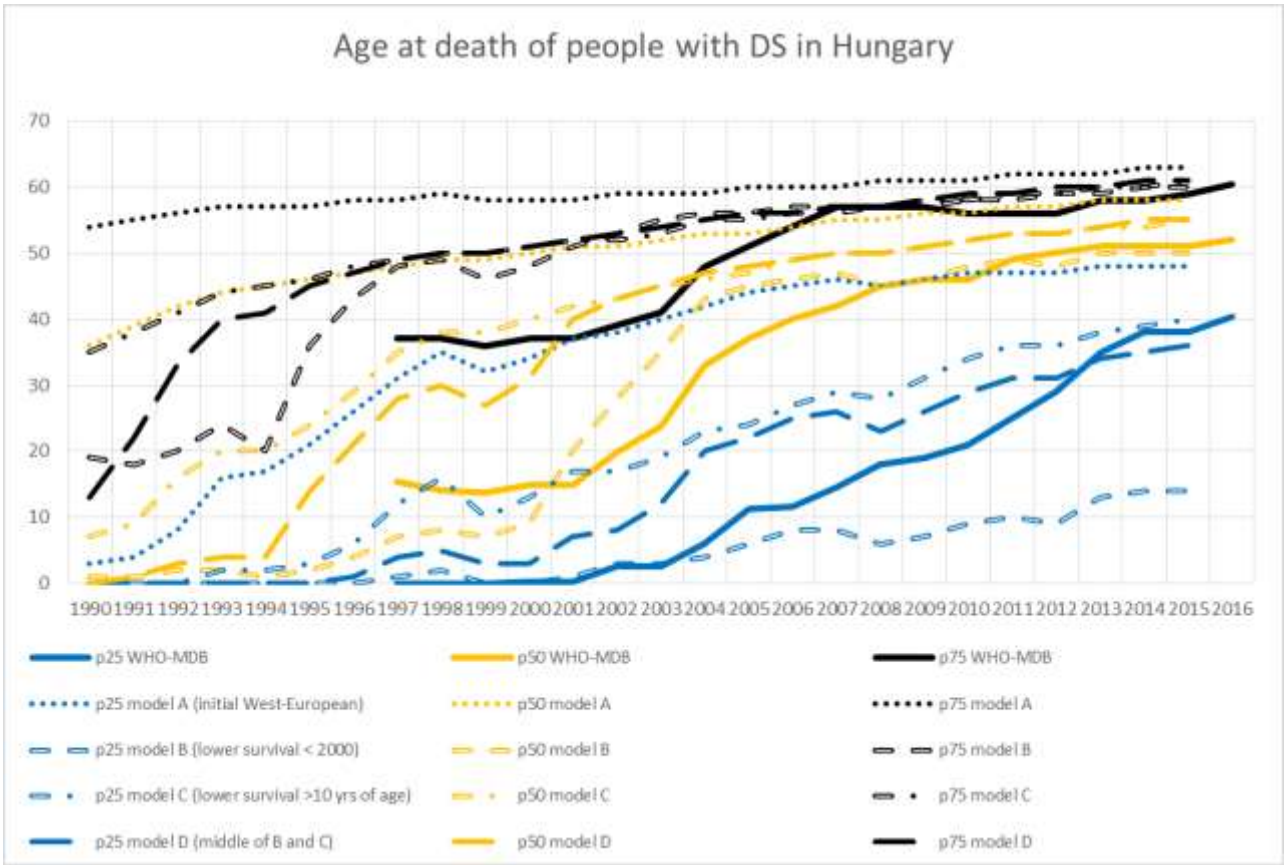
Looking at the graphs on age distribution of deceased people with DS, the best fitting model for 2005–2015 and for 1996–2006 seems to be Models C or D, of which we deem Model D to be more credible.

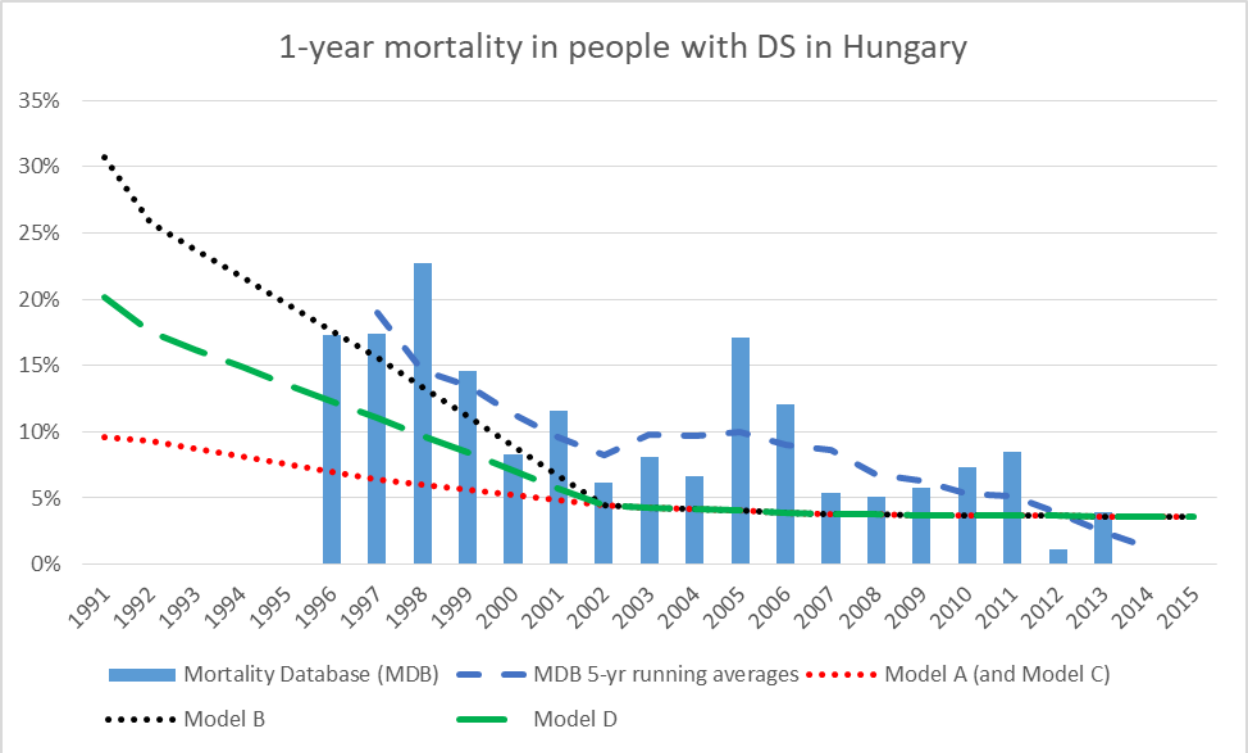
For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.8 ($p < 0.000$). Correlation of MDB with Model B is 0.92 ($p < 0.000$). With Model C, it is 0.93 ($p < 0.000$), and with Model D, it is 0.94 ($p < 0.000$). Model D has the best fit. For 1996–2006, this is respectively 0.35 ($p < 0.16$) for model A, 0.91 ($p < 0.000$) for Model B, 0.84 ($p < 0.000$) for Model C, and 0.91 ($p < 0.000$) for Model D. For this period, Model B and Model D have the best fit.

In 2005–2015, the MDB has 57% of deceased persons with DS in the 45–70 year age range. Model A has 74%, and Model B has 51%. Model C has 63%, and Model D has 61%. Model D has the best fit. In 1996–2006, the MDB value is 24%. Model A predicts 63%, and Model B predicts 32%. Model C predicts 43%, and Model D predicts 41%. In this regard, Model B, followed by Model D, seems to have the best fit for 1996–2006.




Distribution of age at death of people with DS in Hungary, 1996-2006
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
1996-2006 National Statistics - WHO-MDB
1996-2006 model A (initial West European style)
1996-2006 model B (lower survival < 2000)
1996-2006 model C (lower survival > 10 yrs)
1996-2006 model D (middle of B and C)


Age at death of people with DS in Hungary
70
60
50
40
30
20
10
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model A (initial West-European)
p50 model A
p75 model A
p25 model B (lower survival < 2000)
p50 model B
p75 model B
p25 model C (lower survival >10 yrs of age)
p50 model C
p75 model C
p25 model D (middle of B and C)
p50 model D
p75 model D



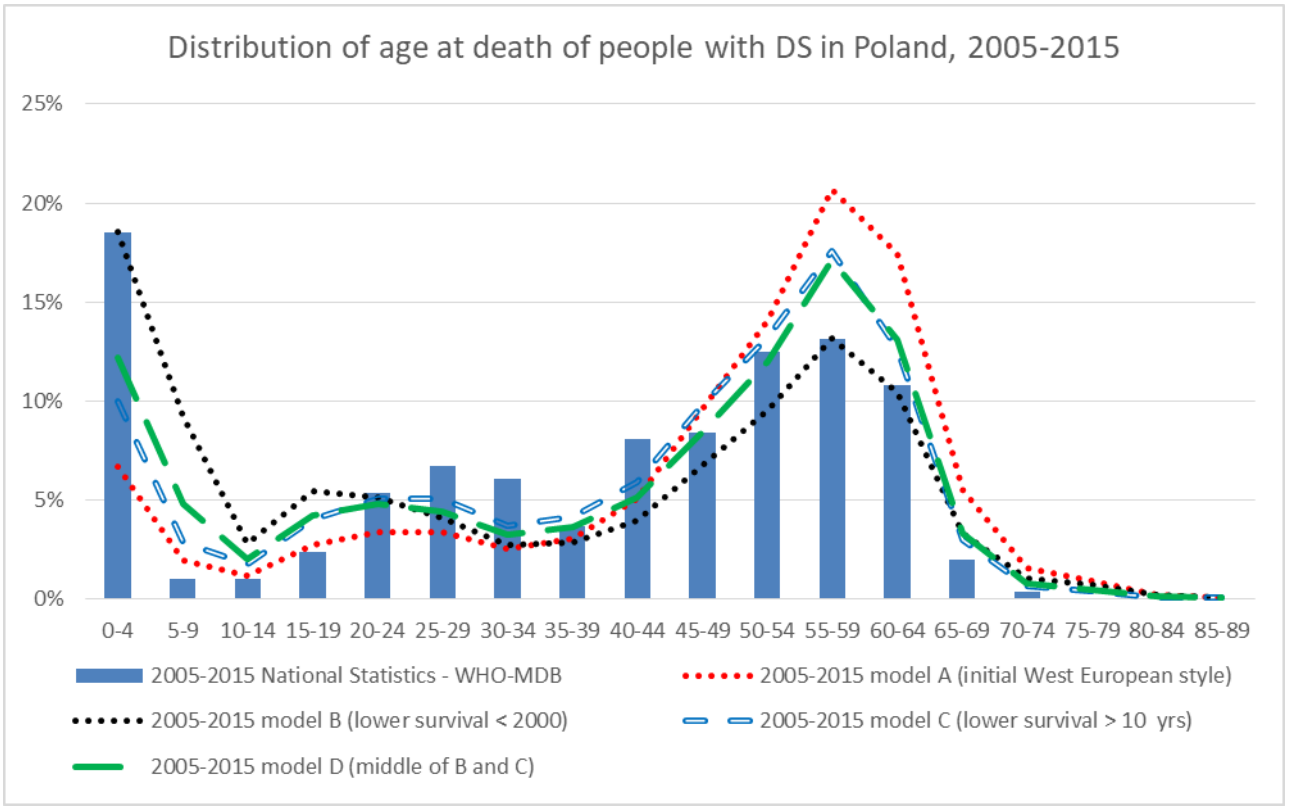
Poland

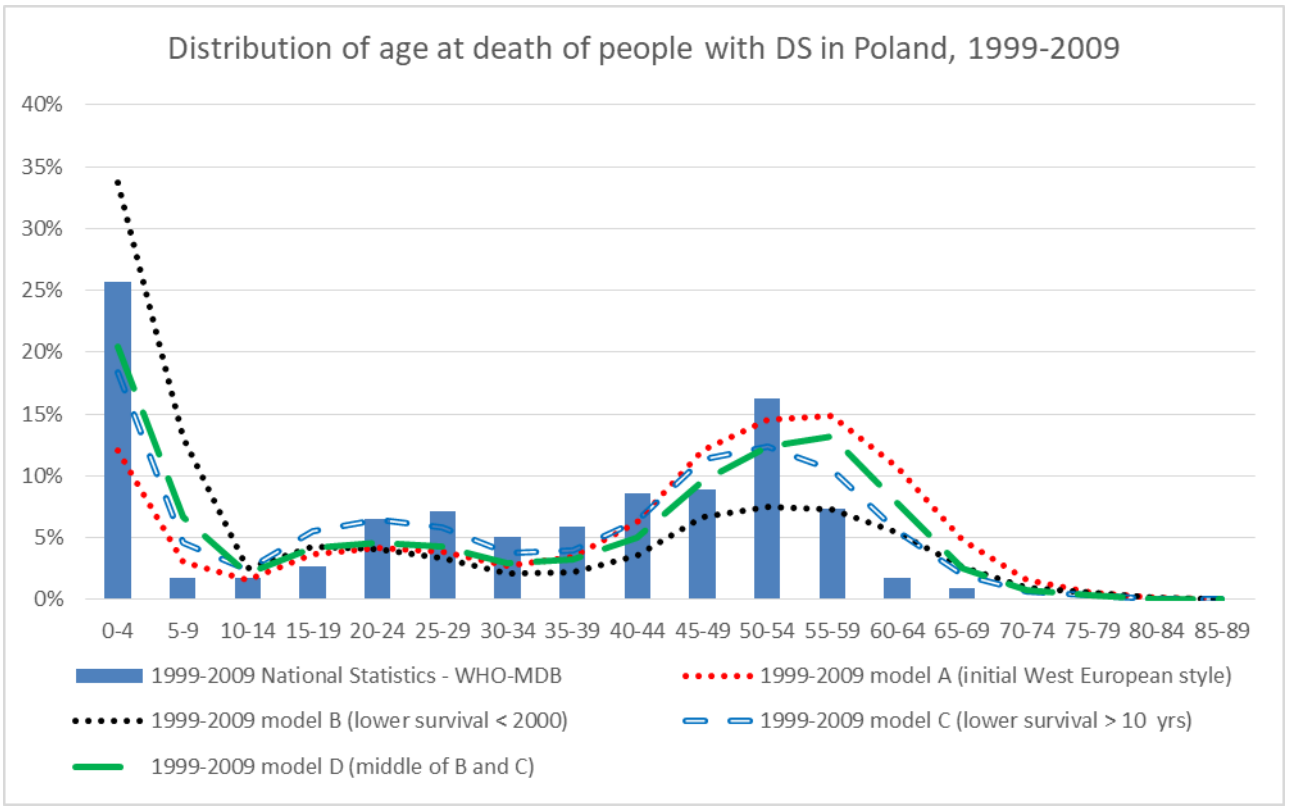
The WHO Mortality Database has data available for 1999–2016. The MDB contains data on 297 people with DS who died between 2005–2015, which is 7% of the number projected by model A (West-European like survival) for the same period, 19% of the number projected by Model B, 10% of Model C, and 12% of Model D. For 1999–2009, this is 339 people, 9% of the projection of model A, 21% of Model B, 14% of Model C, and 16% of Model D.

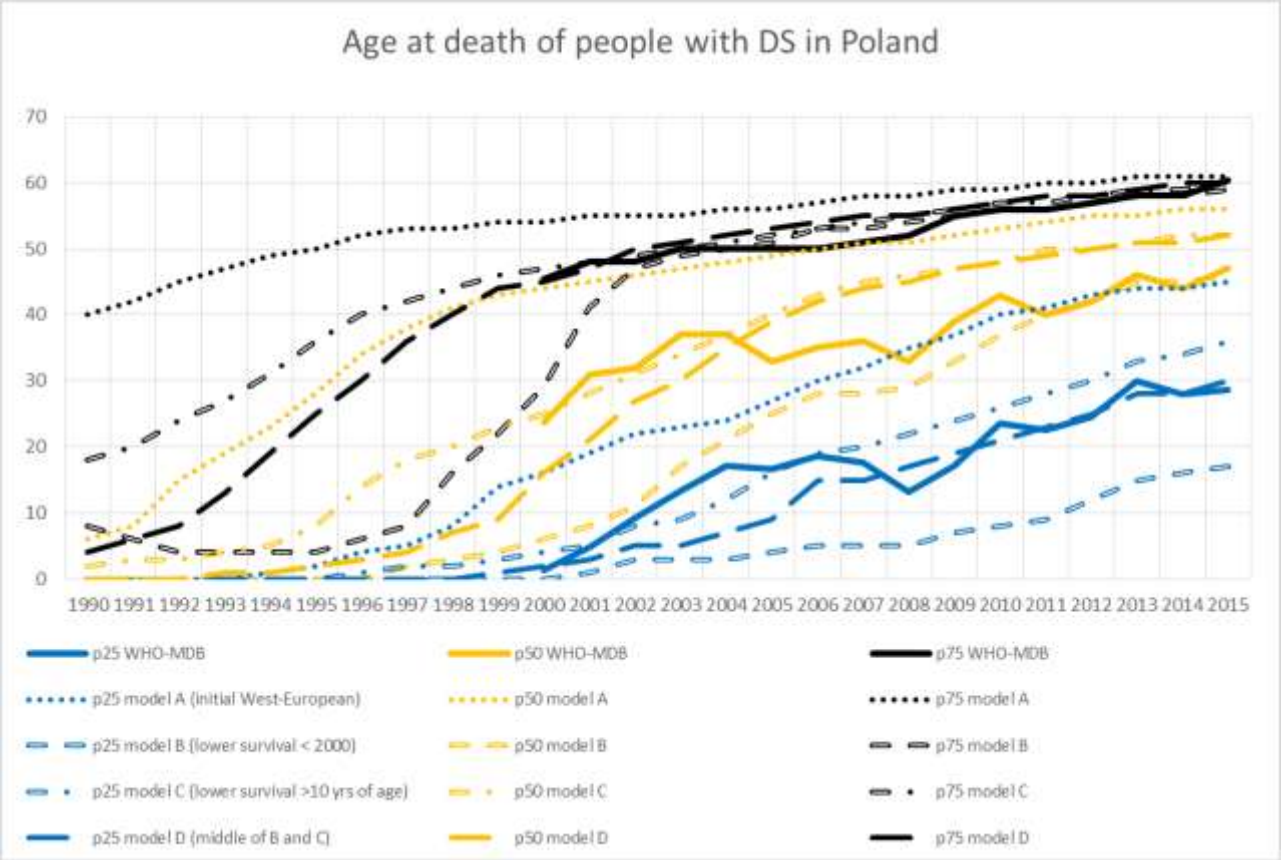
Looking at the graphs on age distribution of deceased people with DS, the best fitting model for 2005–2015 seems to be Model B, and for 1996–2006, it is Models C or D, of which we deem Model D to be more credible.

For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.74 ($p < 0.001$). Correlation of MDB with Model B is 0.86 ($p < 0.000$). With Model C, it is 0.87 ($p < 0.000$), and with Model D, it is 0.89 ($p < 0.000$). Model D has the best fit. For 1999–2009, this is respectively 0.69 ($p < 0.001$) for model A, 0.8 ($p < 0.000$) for Model B, 0.93 ($p < 0.000$) for Model C, and 0.91 ($p < 0.000$) for Model D. For this period, Model C and model D have the best fit.

In 2005–2015, the MDB has 47% of deceased people with DS in the 45–70 year age group. Model A has 67%, and Model B has 43%. Model C has 56%, and Model D has 64%. Model B has the best fit. In 1999–2009, the MDB value is 35%. Model A predicts 57%, and Model B predicts 30%. Model C predicts 42%, and Model D predicts 39%. In this regard, Model D, followed by Model B, seems to have the best fit for 1999–2009.


Distribution of age at death of people with DS in Poland, 2005-2015
25%
20%
15%
10%
5%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
2005-2015 National Statistics - WHO-MDB
2005-2015 model A (initial West European style)
2005-2015 model B (lower survival < 2000)
2005-2015 model C (lower survival > 10 yrs)
2005-2015 model D (middle of B and C)


Distribution of age at death of people with DS in Poland, 1999-2009
40%
35%
30%
25%
20%
15%
10%
5%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
1999-2009 National Statistics - WHO-MDB
1999-2009 model A (initial West European style)
1999-2009 model B (lower survival < 2000)
1999-2009 model C (lower survival > 10 yrs)
1999-2009 model D (middle of B and C)



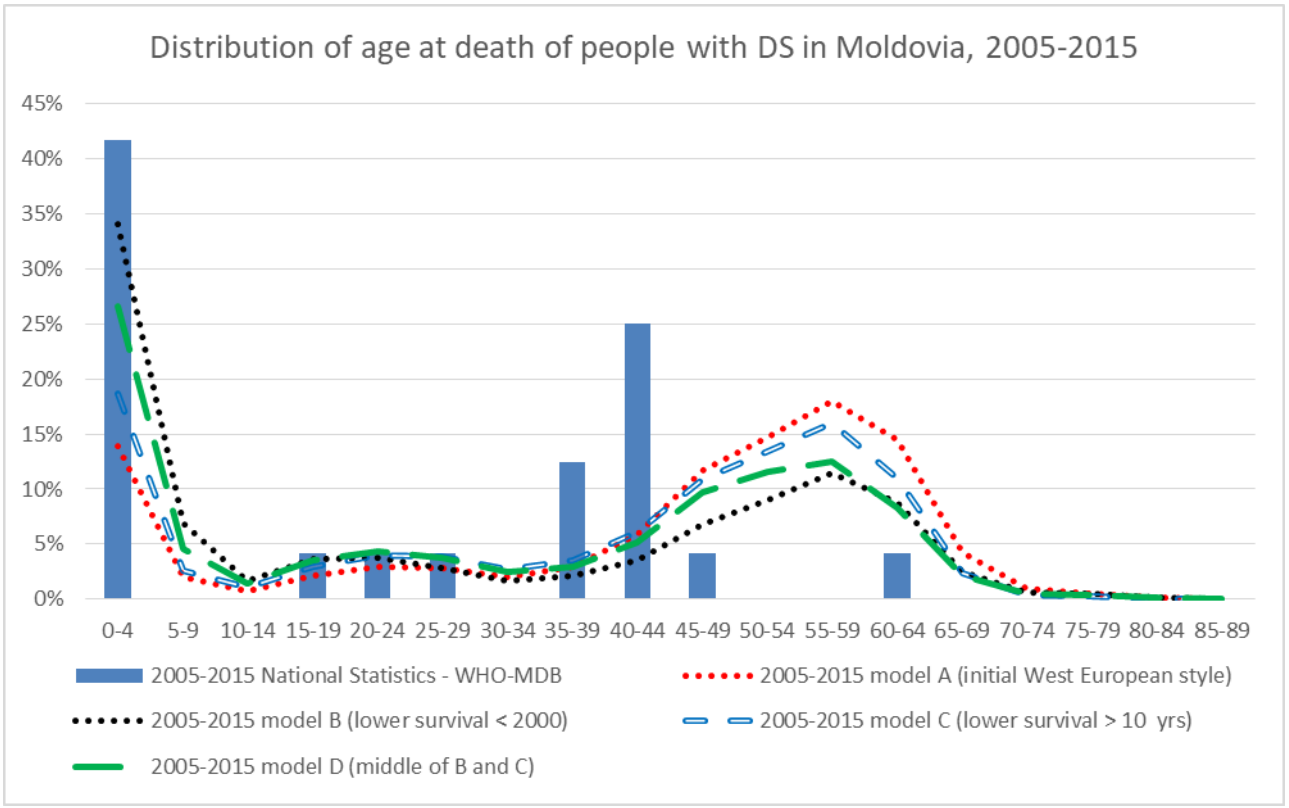
Republic of Moldova

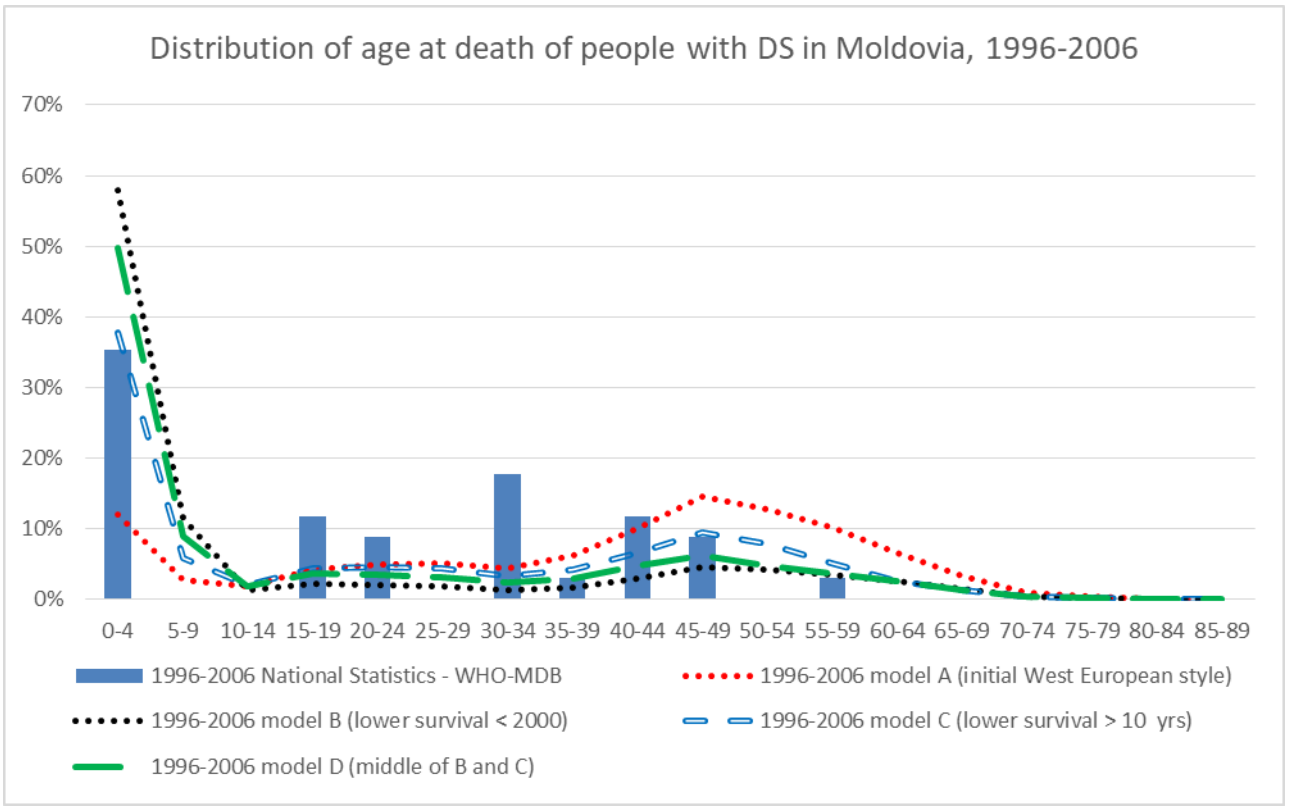
The WHO Mortality Database has data available for 1996–2016. The MDB contains data on 24 people with DS who died between 2005–2015, which is 5% of the number projected by model A (West-European like survival) for the same period, 11% of the number projected by Model B, 6% of Model C, and 9% of Model D. For 1996–2006, this is 34 people, 9% of the projection of model A, 14% of Model B, 11% of Model C, and 13% of Model D.

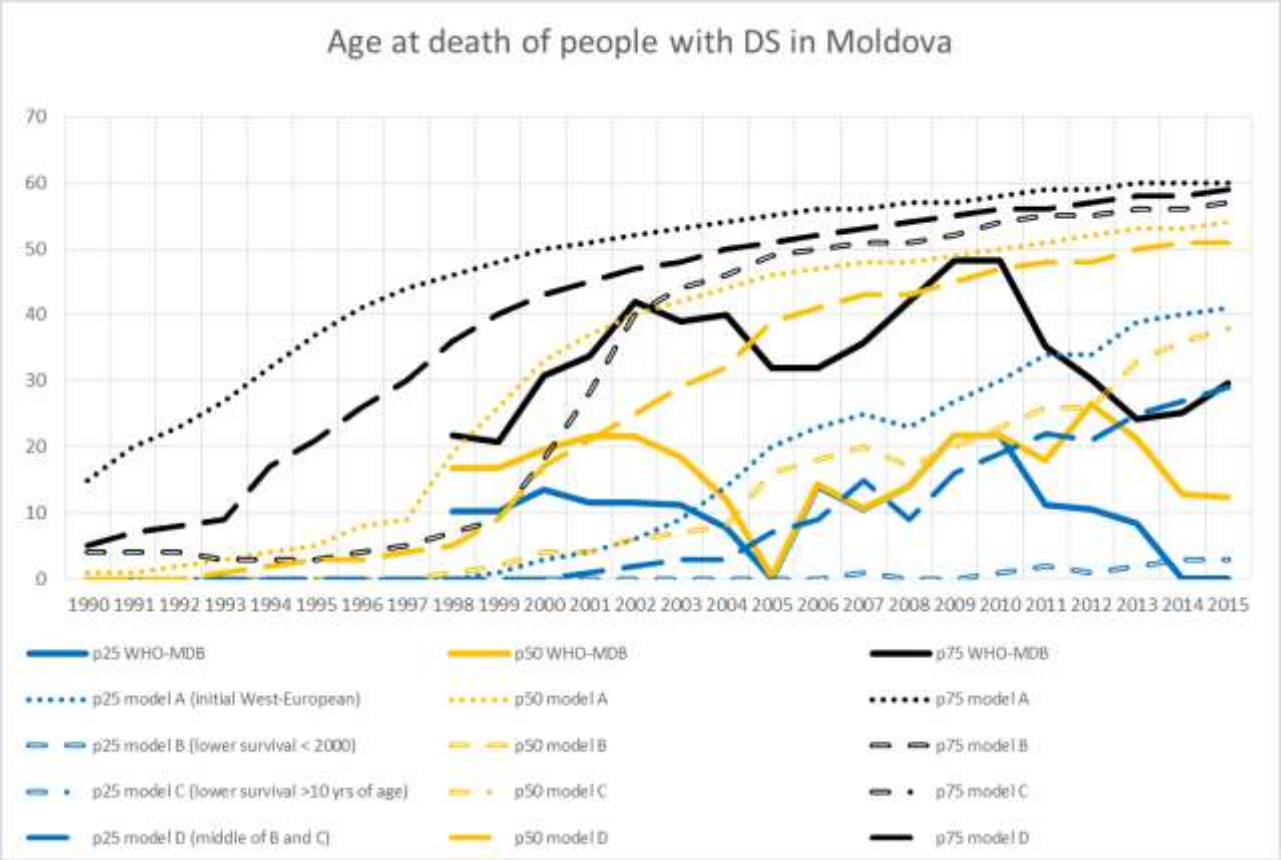
Looking at the graphs on age distribution of deceased people with DS, none of the models seems to have a far better fit than the others, though Model B and Model D appear to have a better fit for 2005–2015.

For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.31 ($p < 0.21$). Correlation of MDB with Model B is 0.74 ($p < 0.000$). With Model C, it is 0.51 ($p < 0.032$), and with Model D, it is 0.7 ($p < 0.001$). Model B has the best fit, followed by Model D. For 1996–2006, this is respectively 0.47 ($p < 0.052$) for model A, 0.79 ($p < 0.000$) for Model B, 0.84 ($p < 0.000$) for Model C, and 0.82 ($p < 0.000$) for Model D. For this period, Model C and Model D have the best fit.

In 2005–2015, the MDB has 8% of deceased persons with DS in the 45–70 year age group. Model A has 63%, and Model B has 39%. Model C has 54%, and Model D has 44%. Model B has the best fit, but discrepancy between MDB and the models is large. In 1996–2006, the MDB value is 12%. Model A predicts 47%, and Model B predicts 16%. Model C predicts 26%, and Model D predicts 19%. In this regard, Model B, followed by Model D, seems to have the best fit for 1996–2006.


Distribution of age at death of people with DS in Moldovia, 2005-2015
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
2005-2015 National Statistics - WHO-MDB
2005-2015 model A (initial West European style)
2005-2015 model B (lower survival < 2000)
2005-2015 model C (lower survival > 10 yrs)
2005-2015 model D (middle of B and C)


Distribution of age at death of people with DS in Moldovia, 1996-2006
70%
60%
50%
40%
30%
20%
10%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
1996-2006 National Statistics - WHO-MDB
1996-2006 model A (initial West European style)
1996-2006 model B (lower survival < 2000)
1996-2006 model C (lower survival > 10 yrs)
1996-2006 model D (middle of B and C)


Age at death of people with DS in Moldova
70
60
50
40
30
20
10
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model A (initial West-European)
p50 model A
p75 model A
p25 model B (lower survival < 2000)
p50 model B
p75 model B
p25 model C (lower survival >10 yrs of age)
p50 model C
p75 model C
p25 model D (middle of B and C)
p50 model D
p75 model D

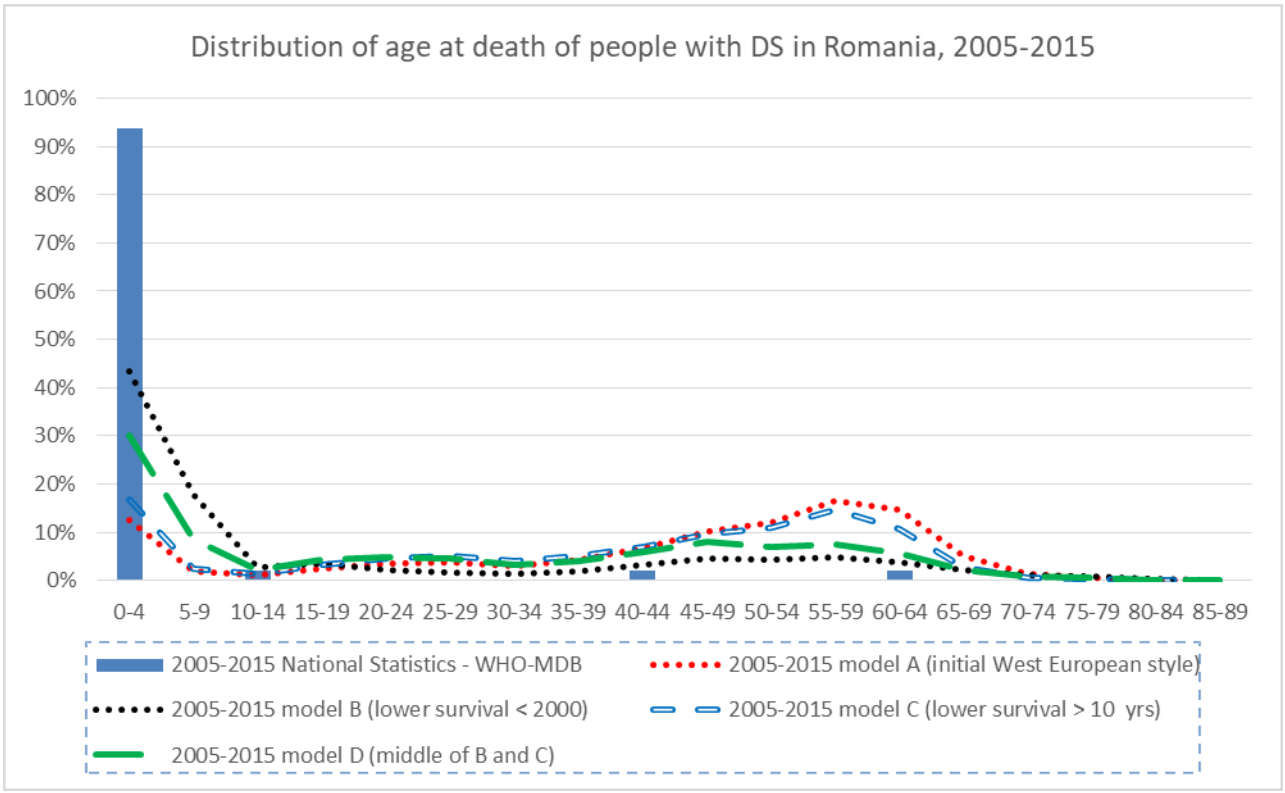
Romania

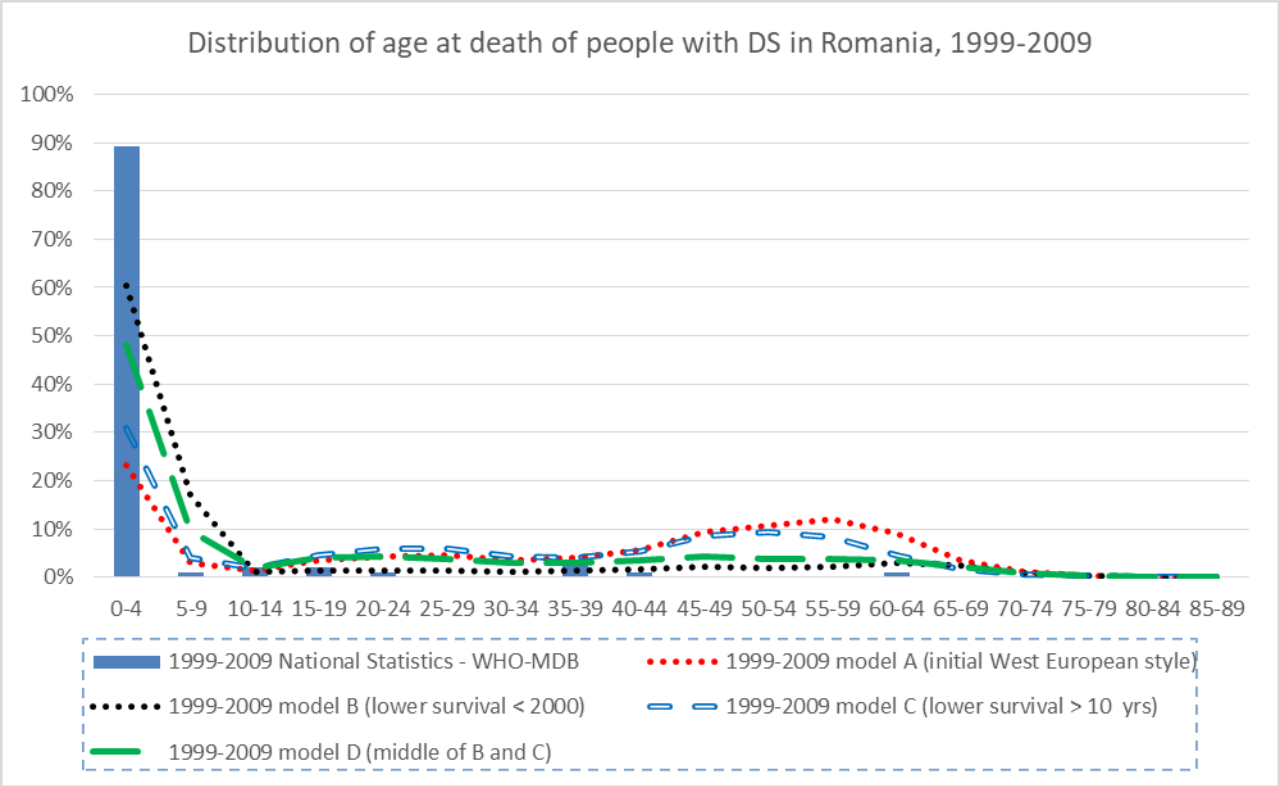
The WHO Mortality Database has data available for 1999–2016. The MDB contains data on 47 people with DS who died between 2005–2015, which is 2% of the number projected by model A (West-European like survival) for the same period, 8% of the number projected by Model B, 3% of Model C, and 6% of Model D. For 1999–2009, this is 102 people, 6% of the projection of model A, 14% of Model B, 8% of Model C, and 11% of Model D.

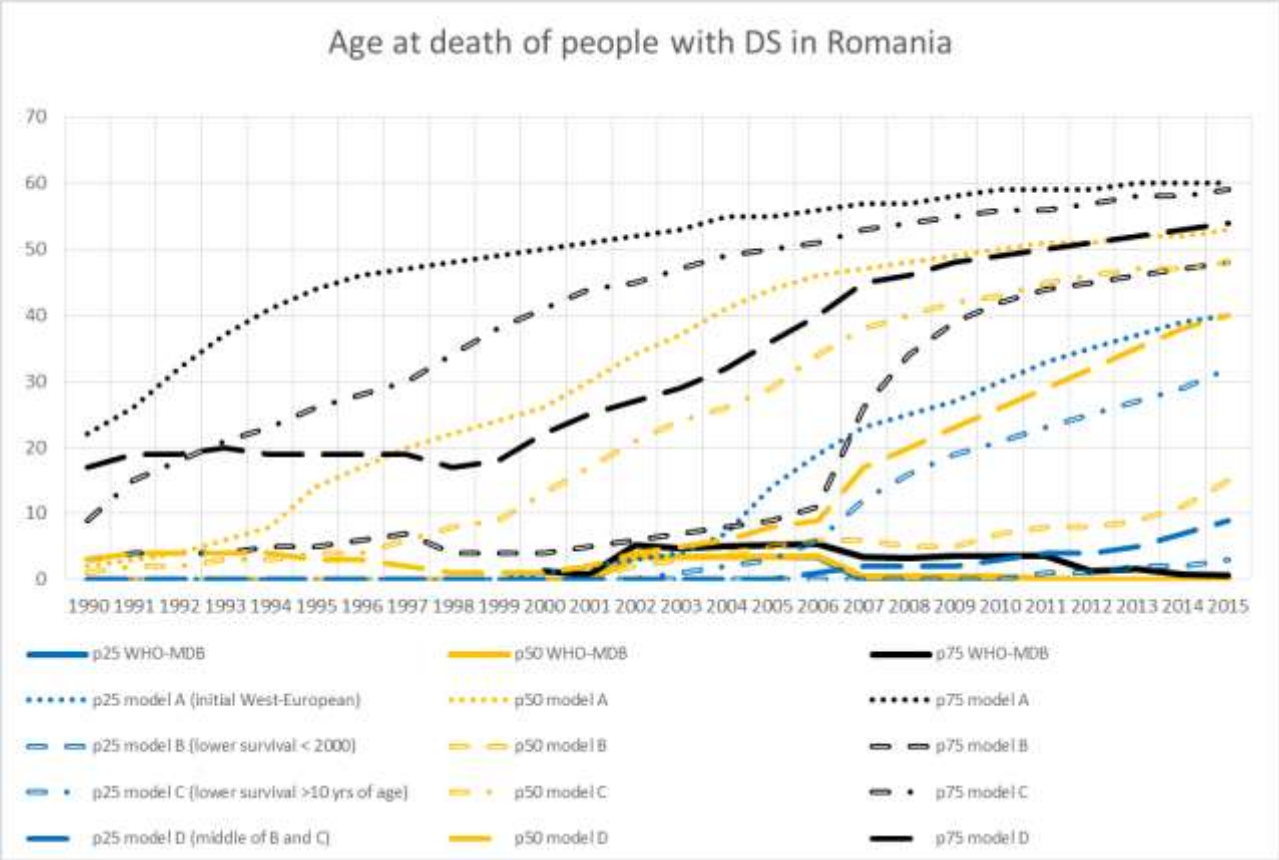
Looking at the graphs on age distribution of deceased people with DS, Model B and Model D appear to have a better fit than Model A or Model C.

For 2005–2015, as regards the age distribution of deceased people with DS, correlation between MDB and model A is 0.34 ($p < 0.17$). Correlation of MDB with Model B is 0.92 ($p < 0.000$). With Model C, it is 0.56 ($p < 0.015$), and with Model D, it is 0.92 ($p < 0.001$). Model B and Model D have the best fit. For 1999–2009, this is respectively 0.77 ($p <0.000$) for model A, 0.97 ($p < 0.000$) for Model B, 0.91 ($p < 0.000$) for Model C, and 0.98 ($p <0.000$) for Model D. For this period, Model D has the best fit, followed by Model B.

In 2005–2015, the MDB has 2% of deceased persons with DS in the 45–70 year age range. Model A has 58%, and Model B has 20%. Model C has 49%, and Model D has 30%. Model B has the best fit, but discrepancy between MDB and the models is large. In 1999–2009, the MDB value is 1%. Model A predicts 45%, and Model B predicts 12%. Model C predicts 32%, and Model D predicts 18%. In this regard, Model B seems to have the best fit for 1996–2006, but discrepancy between MDB and models is large.







Russian Federation

No data are available in the MDB.

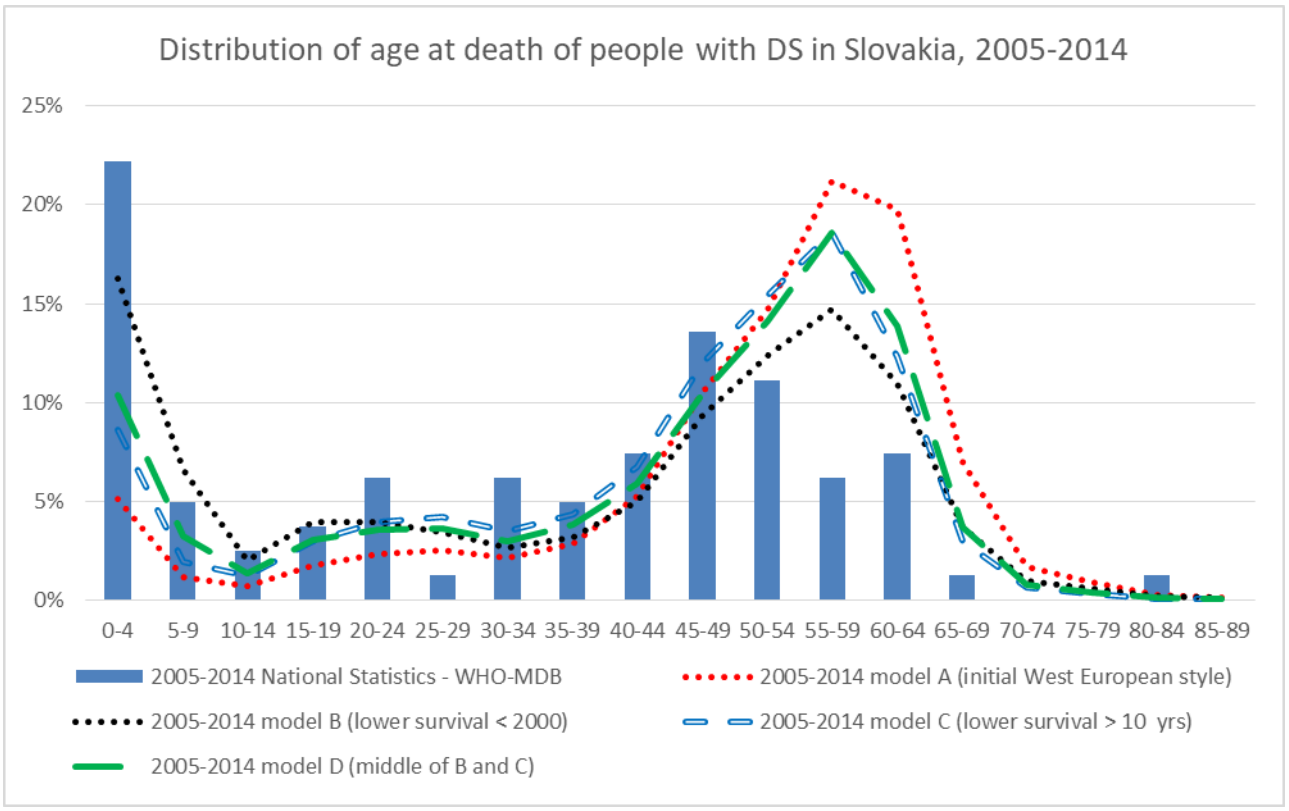
Slovakia

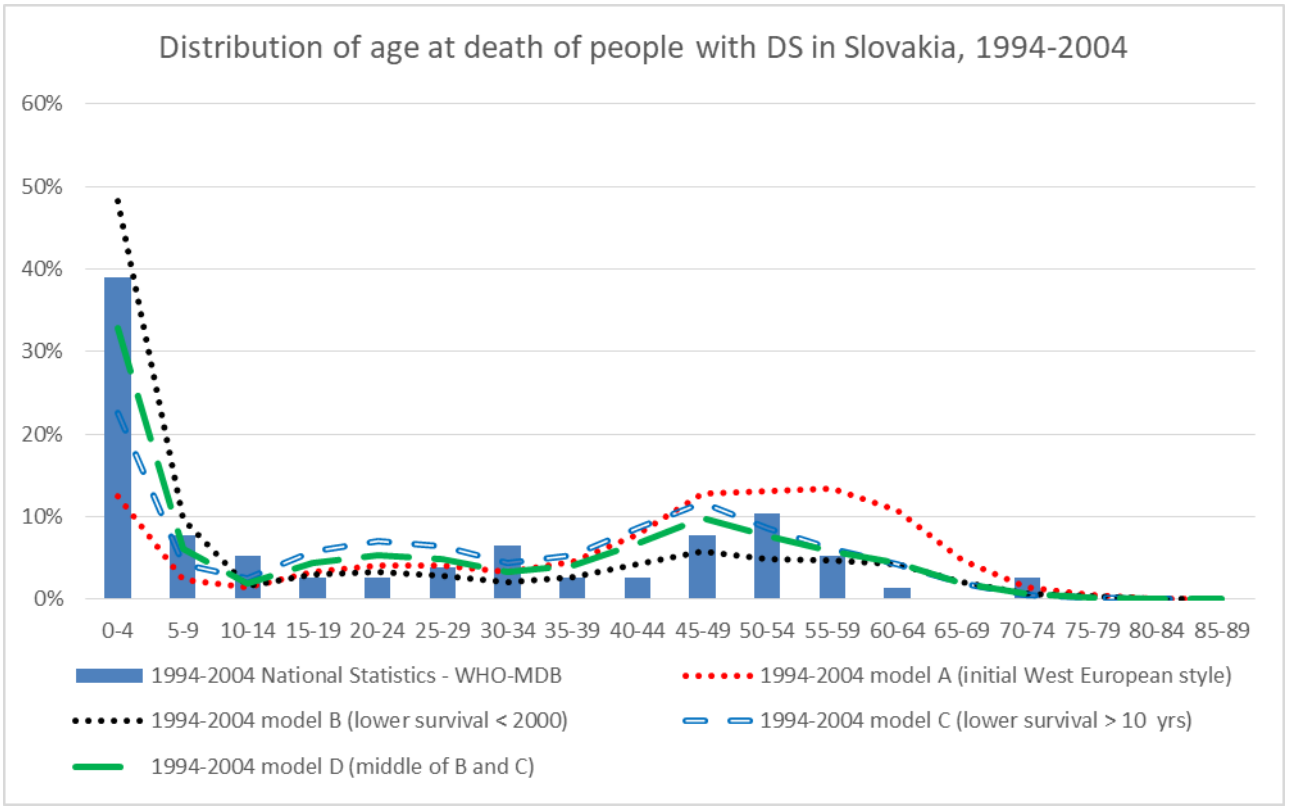
The WHO Mortality Database has data available for 1994–2014. The MDB contains data on 81 people with DS who died between 2005–2014, which is 14% of the number projected by model A (West-European like survival) for the same period, 44% of the number projected by Model B, 24% of Model C, and 29% of Model D. For 1994–2004, this is 77 people, 17% of the projection of model A, 37% of Model B, 32% of Model C, and 33% of Model D.

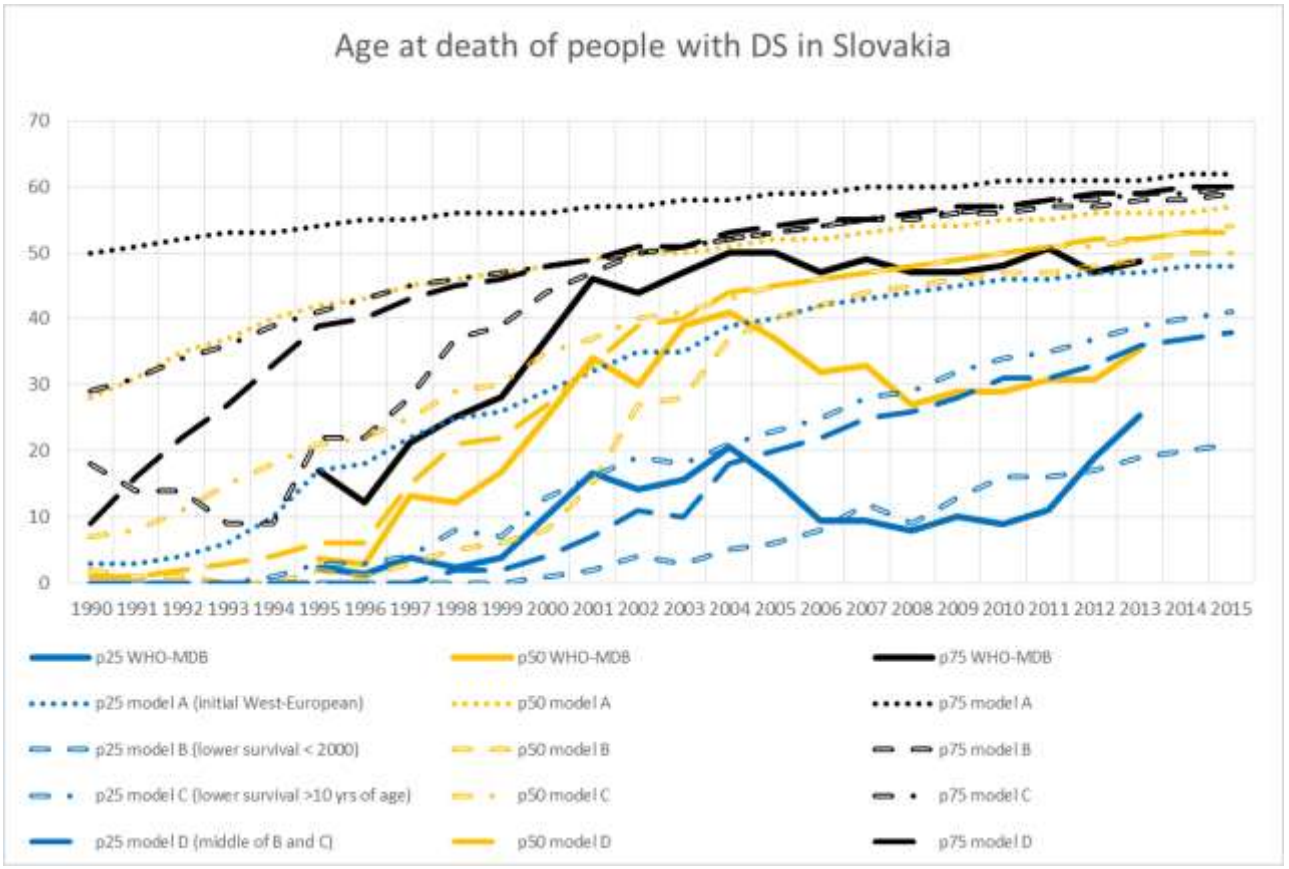
Looking at the graphs on age distribution of deceased people with DS, Model B seems to have the best fit for 2005–2014, and Model C and Model D have the best fit for 1994–2004.

For 2005–2014, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.39 ($p < 0.11$). Correlation of MDB with Model B is 0.82 ($p < 0.000$). With Model C, it is 0.61 ($p < 0.007$), and with Model D, it is 0.65 ($p < 0.004$). Model B has the best fit. For 1994–2004, this is respectively 0.51 ($p < 0.033$) for model A, 0.97 ($p < 0.000$) for Model B, 0.88 ($p < 0.000$) for Model C, and 0.96 ($p < 0.000$) for Model D. For this period, Model B has the best fit, followed by Model D.

In 2005–2014, the MDB has 40% of deceased people with DS in the 45–70 year age group. Model A has 73%, and Model B has 51%. Model C has 61%, and Model D has 60%. Model B has the best fit. In 1994–2004, the MDB value is 25%. Model A predicts 55%, and Model B predicts 22%. Model C predicts 32%, and Model D predicts 30%. In this regard, Model B seems to have the best fit for 1994–2004, followed by Model D.




Distribution of age at death of people with DS in Slovakia, 1994-2004
60%
50%
40%
30%
20%
10%
0%
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89
1994-2004 National Statistics - WHO-MDB
1994-2004 model A (initial West European style)
1994-2004 model B (lower survival < 2000)
1994-2004 model C (lower survival > 10 yrs)
1994-2004 model D (middle of B and C)


Age at death of people with DS in Slovakia
70
60
50
40
30
20
10
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
p25 WHO-MDB
p50 WHO-MDB
p75 WHO-MDB
p25 model A (initial West-European)
p50 model A
p75 model A
p25 model B (lower survival < 2000)
p50 model B
p75 model B
p25 model C (lower survival >10 yrs of age)
p50 model C
p75 model C
p25 model D (middle of B and C)
p50 model D
p75 model D

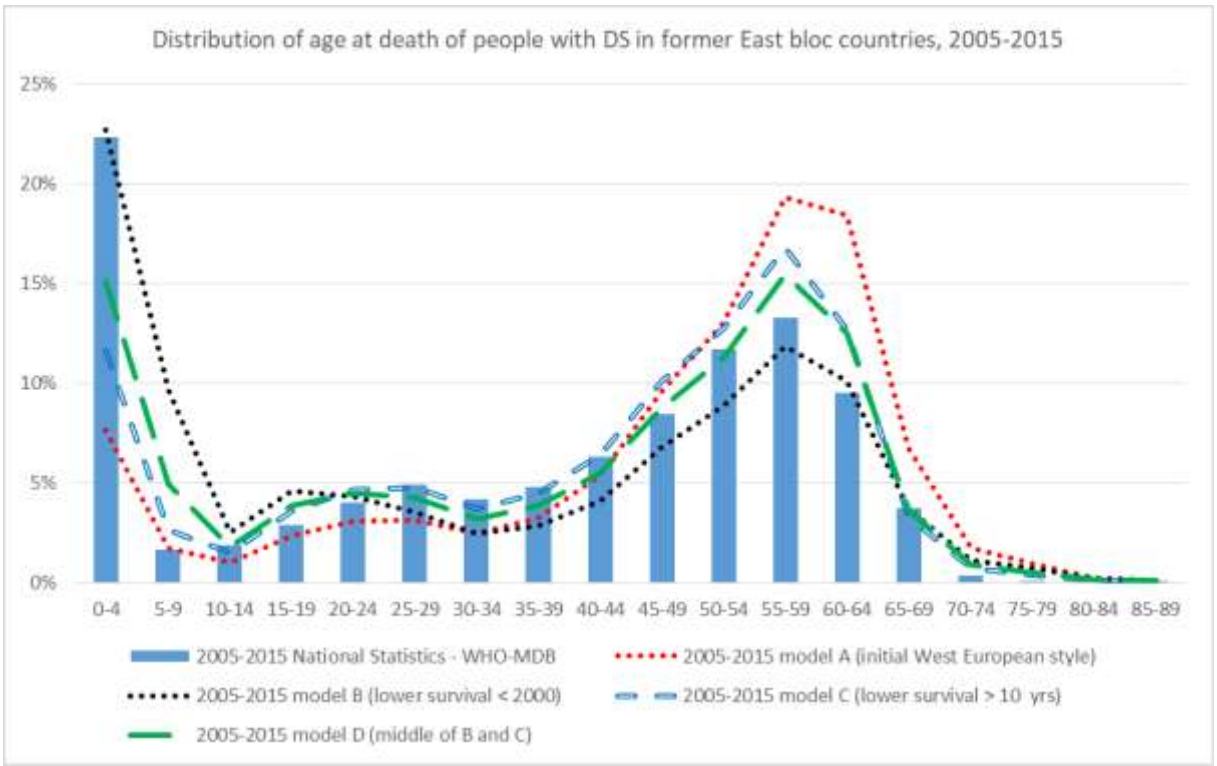
Ukraine
No data are available in the MDB.

All former East bloc countries pooled

For most comparisons of the individual countries, Model D has the best fit; for some others, it is Model B. So, whether Model B or Model D is the most appropriate model seems to be inconclusive. To further explore the data, we have pooled the data for all former East bloc countries. We have excluded Albania, Russia, Belarus, and Ukraine from the modeling, as there are no data on DS for these countries in the MDB.

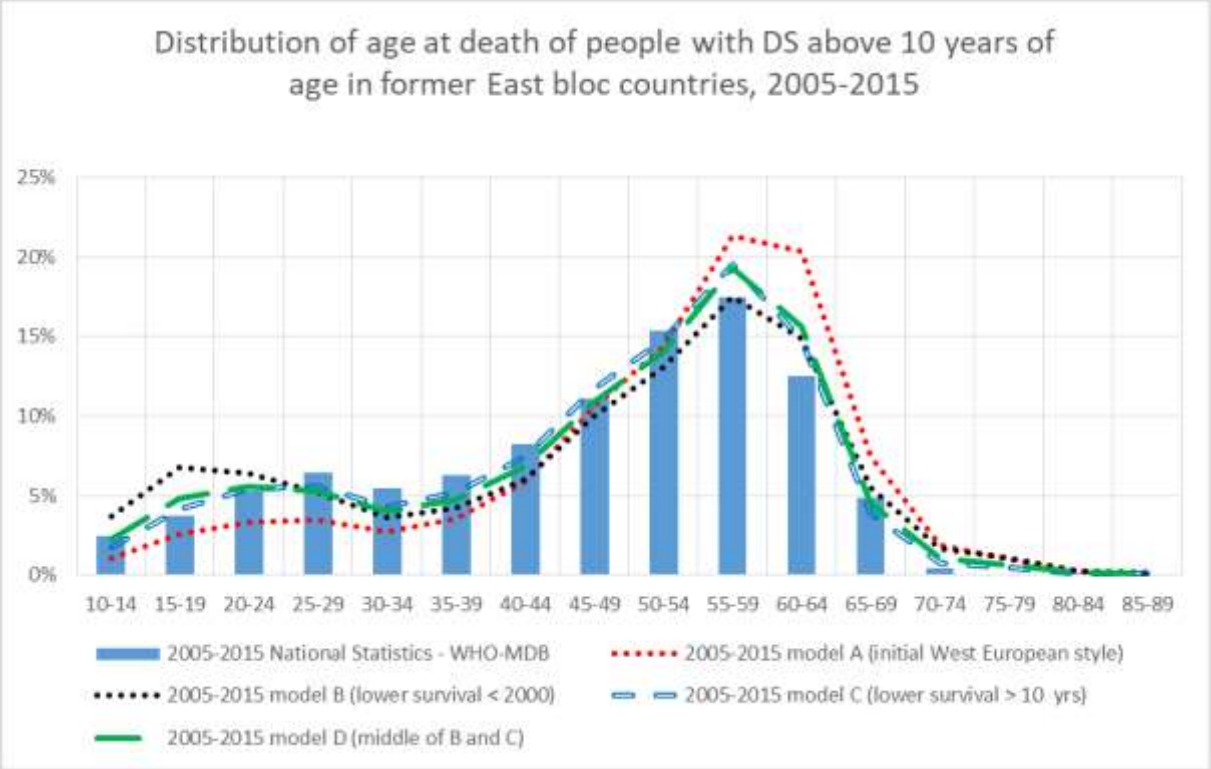
Pooled for 2005–2015, the MDB has information on 1,732 deceased people with DS in former East bloc countries, which is 14% of the number predicted by model A, 40% of Model B, 21% of Model C, and 27% of Model D. Looking at the graph below, the best fitting model seems to be Model C or Model D, with Model D fitting better in regards to the percentage in the 0–4 year age group. In addition, we think that a model that assumes a poorer survival, but only for those above 10 years of age, is not fully credible. Model A has the poorest fit.

For 2005–2015, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.69 ($p < 001$). Correlation of MDB with Model B is 0.91 ($p < 0.000$). With Model C, it is 0.86 ($p < 0.000$), and with Model D, it is 0.93 ($p < 0.000$). Model D has the best fit. As a comparison, for the former West bloc countries, the correlation between Model D and MDB was 0.98.



Historically, we have seen that the survival of children with DS up to 10 years of age has changed considerably. The modeled number of deceased children up to this age is very much dependent on how these survival rates are modeled. Secondly, it is possible that the chance for a deceased person with DS to be reported as having died with DS as the primary cause of death is higher in very young

children, so these might be relatively "over-represented" in the MDB. Finally, relatively more deaths are in the young age groups, so errors in modeling or "over-representation" in the empirical data will affect the whole graph. That is why we have analyzed the age distribution again for people with DS 10 years of age or older separately (see the graph below).



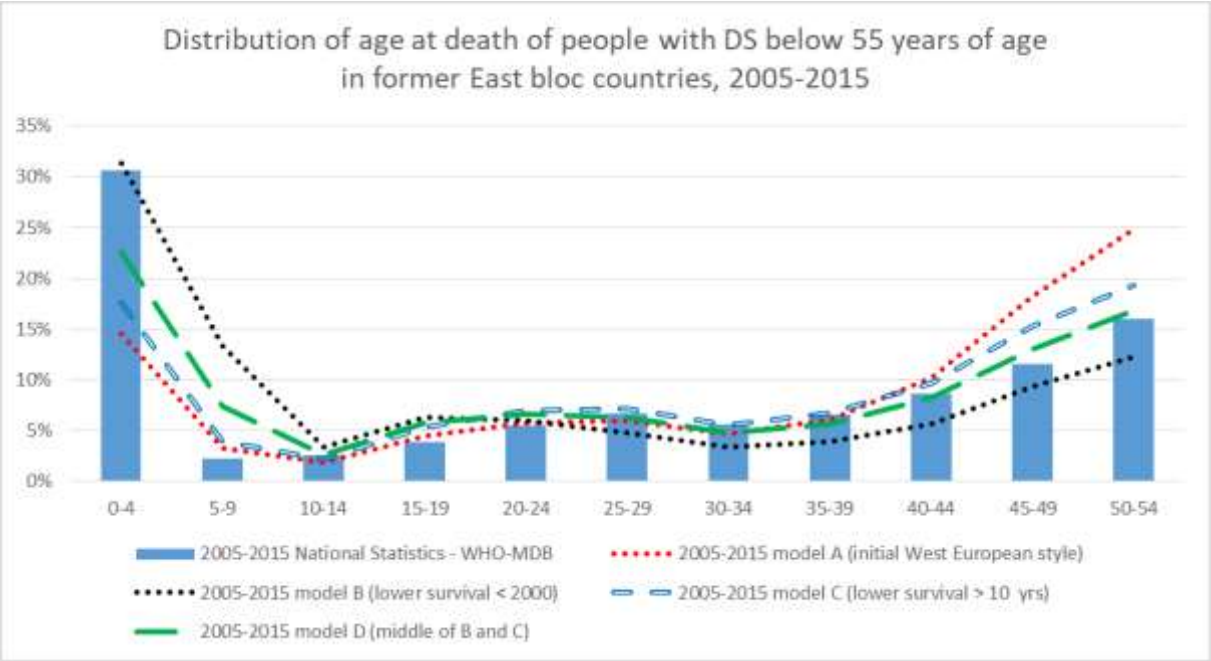
Pooled for 2005–2015, the MDB has information on 1,306 deceased people with DS of 10 years or above in former East bloc countries , which is 11% of the number predicted by model A, 45% of Model B, 18% of Model C, and 25% of Model D. Looking at the graph above, the best fitting model seems to be Model C or Model D. For 2005–2015, in regards to the age distribution of deceased people with DS of 10 years or above, correlation between MDB and model A is 0.92 (p < 000). Correlation of MDB with Model B is 0.95 (p <0.000). With Model C, it is 0.99 (p < 0.000), and with Model D, it is 0.98 (p < 0.000). Model C and Model D have the best fit. As explained earlier, we deem Model C less likely. As a comparison, for the former West bloc countries, correlation between model and MDB for this age group was 0.99.

In both graphs above, one can see that the difference between Model A and the other models, and between Model A and the MDB data, seems to be that numbers of deceased people above 55 years of age (i.e., born before ~1955) are much higher in Model A. However, we know that there are large differences in how survival rates are modeled in the different models after ~1955, and we would like to know which model captures this best. If we limit the analysis of age distribution to only people under 55 years of age in 2005–2015 (i.e., born after ~1955), which model has the best fit?

Pooled for 2005–2015, the MDB has information on 1,252 deceased people with DS under 55 years of age in former East bloc countries, which is 19% of the number predicted by model A, 40% of Model B, 23% of Model C, and 29% of Model D.

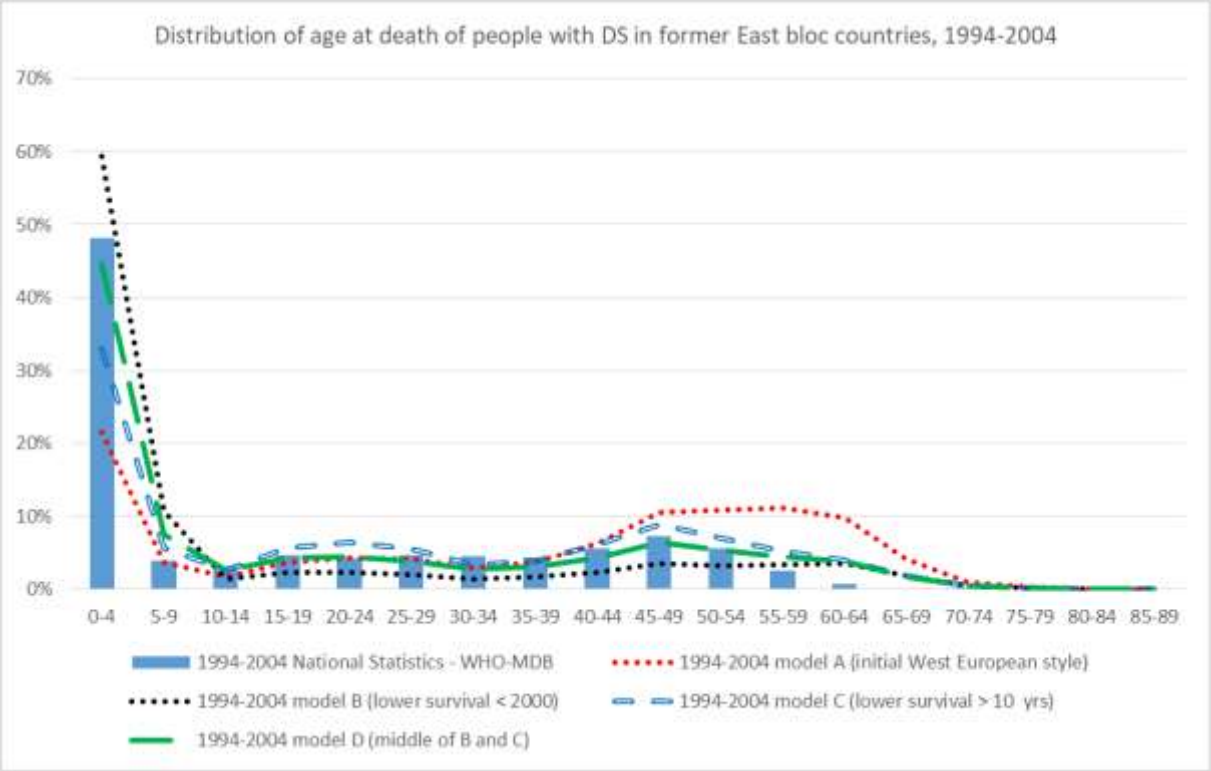
In the graph below, Model D appears to have the best fit. For 2005–2015, in regards to the age distribution of deceased people with DS under 55 years of age, correlation between MDB and model A is 0.68 (p < 021). Correlation of MDB with Model B is 0.87 (p < 0.001). With Model C, it is 0.85 (p <

0.000), and with Model D, it is 0.95 ($p < 0.000$). So, Model D indeed has the best fit. As a comparison, for the former West bloc countries, correlation between this model and MDB for this age group was 0.95, too.

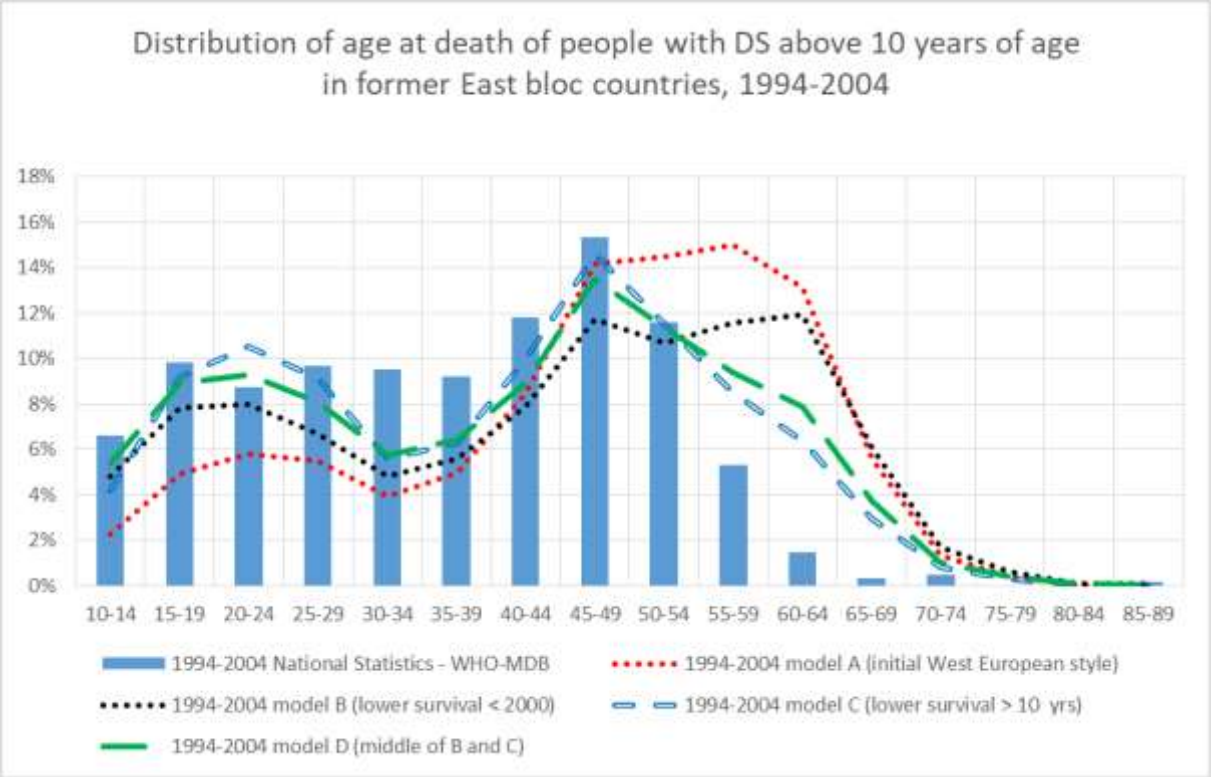


Repeating these analyses for the data from 1994–2004 (yields the following results: the MDB has pooled information on 1,294 deceased people with DS in former East bloc countries, which is 13% of the number predicted by model A, 22% of Model B, 21% of Model C, and 21% of Model D projections (but the MDB does not contain information on all these countries for all the years of birth in this period).

For 1994–2004, in regards to the age distribution of deceased people with DS, correlation between MDB and model A is 0.79 ($p < 0.000$). Correlation of MDB with Model B is 0.98 ($p < 0.000$). With Model C, it is 0.98 ($p < 0.000$), and with Model D, it is 0.99 ($p < 0.000$). Model D has the best fit. As a comparison, for the former West bloc countries, correlation between model and MDB was 0.97.

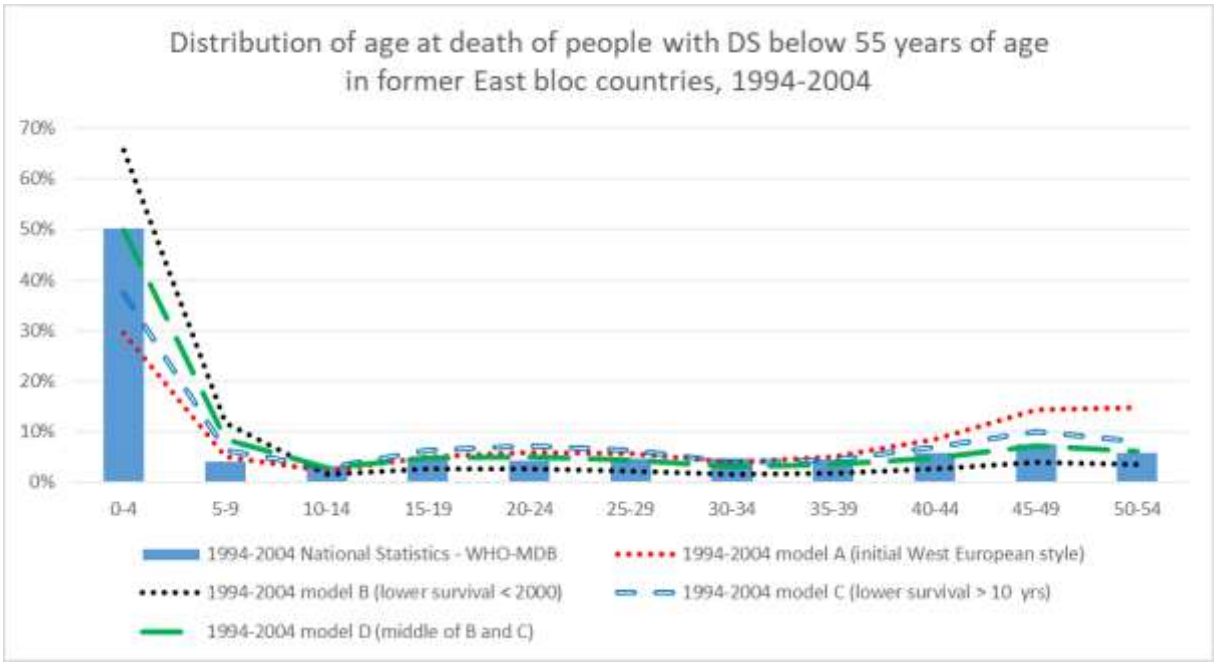


Pooled for 1994–2004, the MDB has information on 620 deceased people with DS of 10 years of age or older in former East bloc countries, which is 9% of the number predicted by model A, 35% of Model B, 16% of Model C, and 21% of Model D. Looking at the graph below, though none of the models has a perfect fit, the best fitting models seem to be Model C and Model D. For 1994–2004, in regards to the age distribution of deceased people with DS of 10 years of age or older, correlation between MDB and model A is 0.52 ($p < 0.041$). Correlation of MDB with Model B is 0.61 ($p < 0.0012$). With Model C, it is 0.9 ($p < 0.000$), and with Model D, it is 0.85 ($p < 0.000$). Model C and Model D have the best fit. As explained earlier, we deem Model C less likely. As a comparison, for the former West bloc countries, correlation between model and MDB for this age group was 0.97.

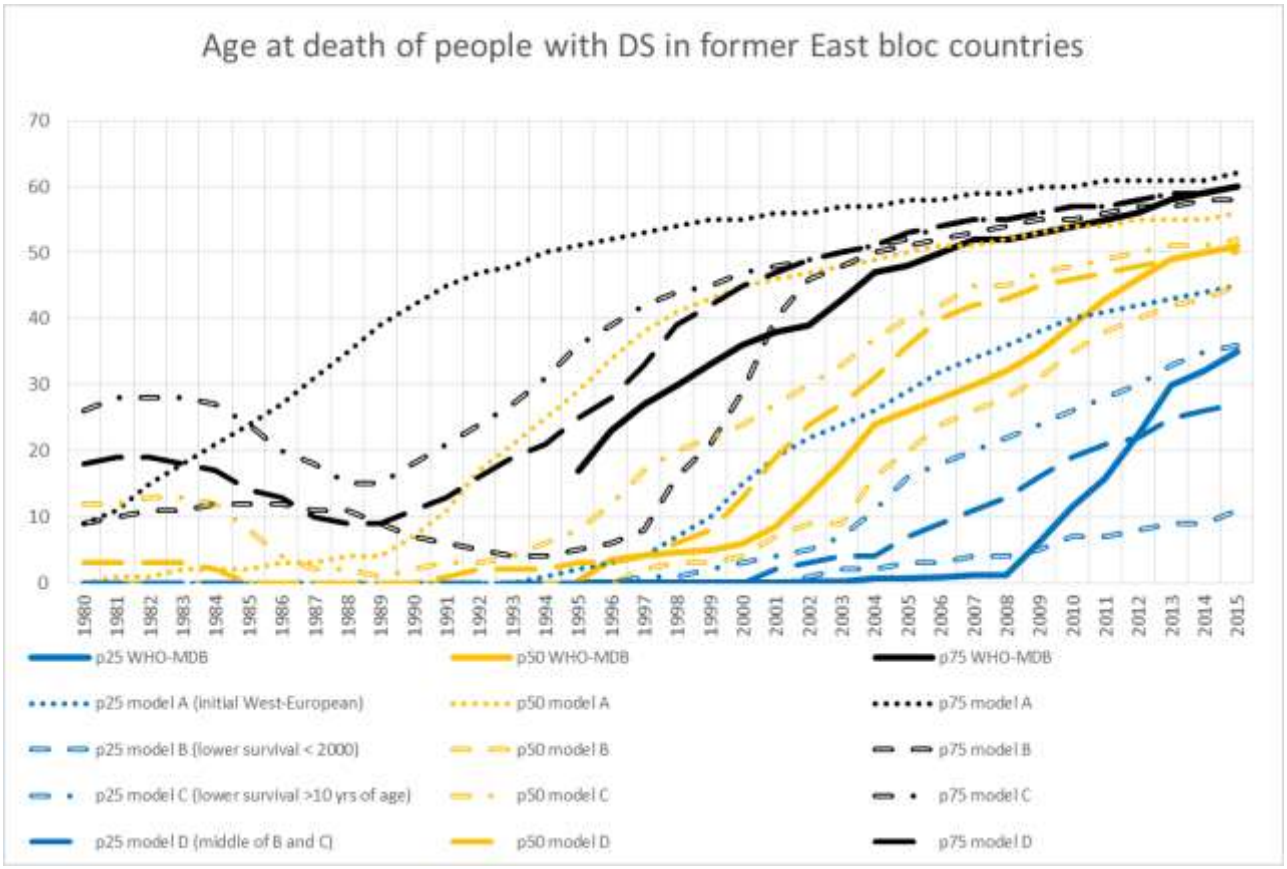


Pooled for 1994–2004, the MDB has information on 1,246 deceased people with DS under 55 years of age in former East bloc countries, which is 18% of the number predicted by model A, 23% of Model B, 23% of Model C, and 22% of Model D.

In the graph below, Model D appears to have the best fit. For 1994–2004, in regards to the age distribution of deceased people with DS under 55 years of age, correlation between MDB and model A is 0.8 ($p < 0.000$). Correlation of MDB with Model B is 0.97 ($p < 0.000$). With Model C, it is 0.98 ($p < 0.000$), and with Model D, it is 0.99 ($p < 0.000$). So, Model D has the best fit. As a comparison, for the former West bloc countries, correlation between model and MDB for this age group was 0.95.



Finally, the graph below presents the age at death of people with DS in former East bloc countries, showing that Model B and Model D have a better fit with the MDB than Model A and Model C.



S6. Results by country

In this section, we present the results by country, that is estimations of number of LBs with DS by year (actual and absent elective terminations), LB prevalence for DS, numbers of people with DS alive by age group, and population prevalence, both historically and currently.

Population prevalence, the number of people with DS alive per 10,000 inhabitants, was estimated by dividing the estimated numbers of people of DS by year by the number of people in general population by year, both for the total group and by age group. The general population numbers were derived from: File POP/1-1: Total population (both sexes combined) by region, subregion and country, annually for 1950-2100 (thousands), and File POP/7-1: Total population (both sexes combined) by five-year age group, region, subregion and country, 1950-2100 (thousands), both from the World Population Prospects of the United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, DVD Edition. https://population.un.org/wpp/Download/Standard/Population/ (retrieved 4-July-2018).

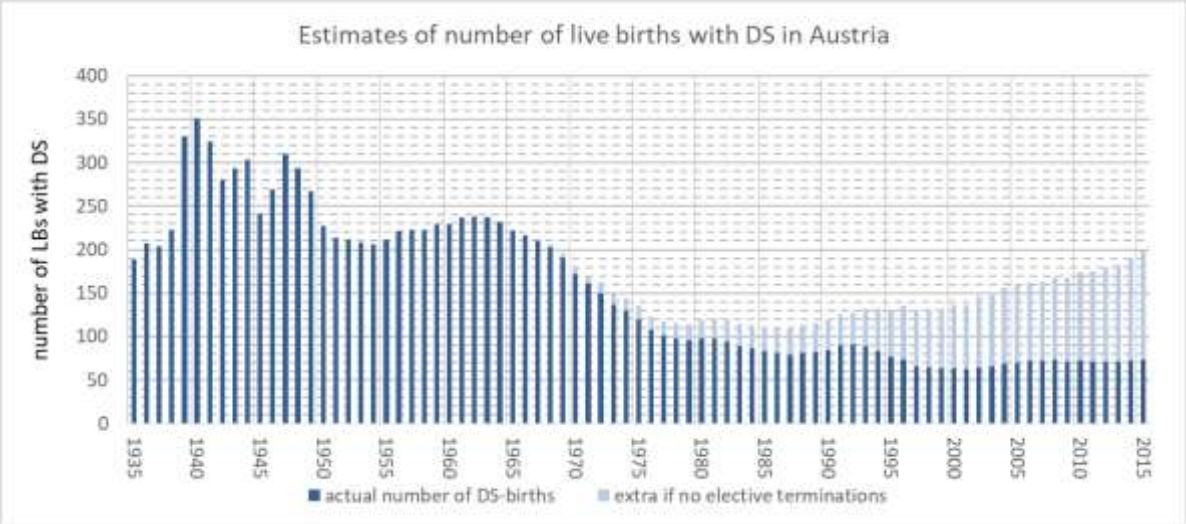
For the former West bloc countries, we have used model A for survival in people with DS (Supplementary Materials S4), as this model has a good fit with data on people with DS alive (from four countries from former West bloc countries with data available) (Supplementary Materials S5A), and with data on age distribution of deaths with DS (S5C) from national statistics in former West bloc countries.

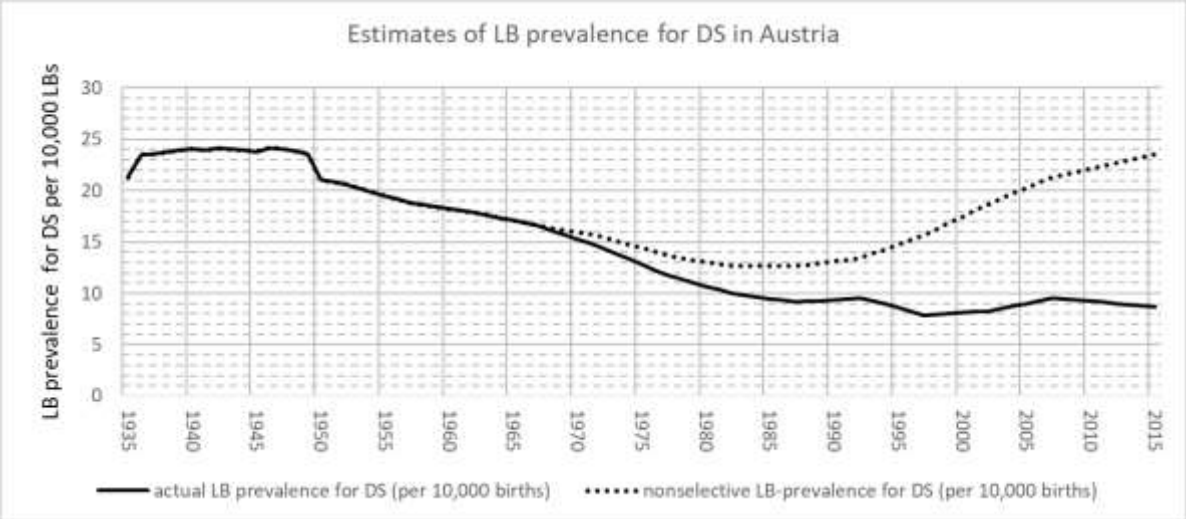
For the former East bloc countries, model A is highly unlikely. Model A has a very poor fit with the data on people with DS alive (from four former East bloc countries with data available) (S5A), and with data on age distribution of deaths with DS (S5C). The alternative Model C is unlikely, as we deem a model in which only survival above 10 years of age is lowered as not credible. Model B has been constructed in such a way that it fits the empirical data on people with DS (S5A and S5B) alive in four former East bloc countries with data available. Model D is an intermediate variant in which survival above 10 years of age up to 1980 is less favorable (as it is in Model C), but 1-year survival is adapted to a value that is the mean of the value of model A (which is the same value as in Model C) and Model B. Model D projects higher numbers in the adult range than found in the empirical data on people alive (S5B), and, if Model D is correct, this would imply that under-ascertainment in these data is much higher in adults than in children. Both Model B and Model D have a better fit to empirical data on age distribution of deaths with DS (S5B) in former East bloc countries than model A. As regards the individual countries, for most comparisons, Model D has the best fit, for some others Model B. Pooling all the data from former East bloc countries together, Model D has the best fit (S5C).

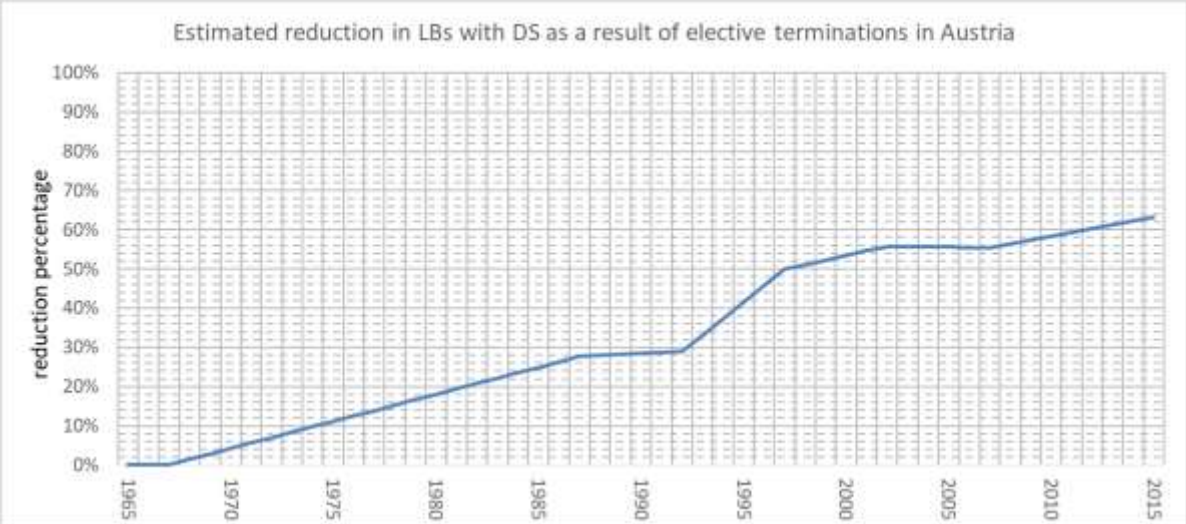
For the former East bloc countries, as regards model A and Model C, we will mention the total number of estimated people with DS alive as of 2015, and the corresponding population prevalence per 10,000 inhabitants. However, the graphs with detailed information on people with DS by age group, both historically and currently, are only presented for Model B and D.

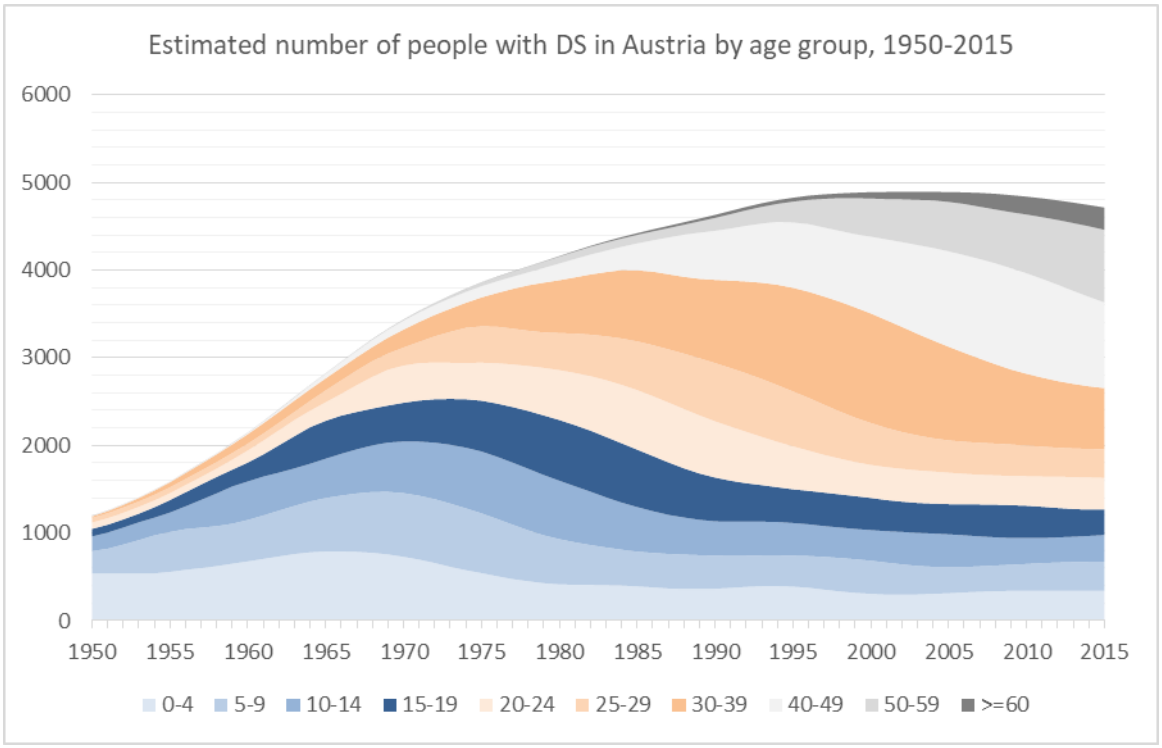
Western Europe

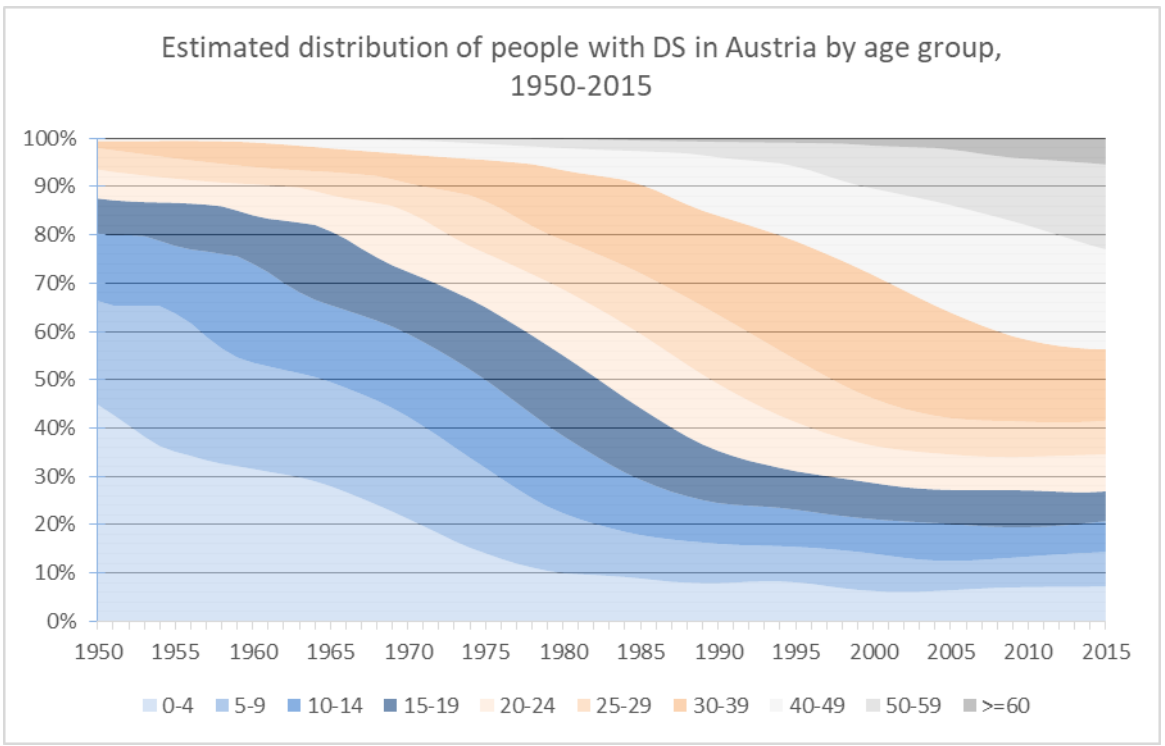
Austria

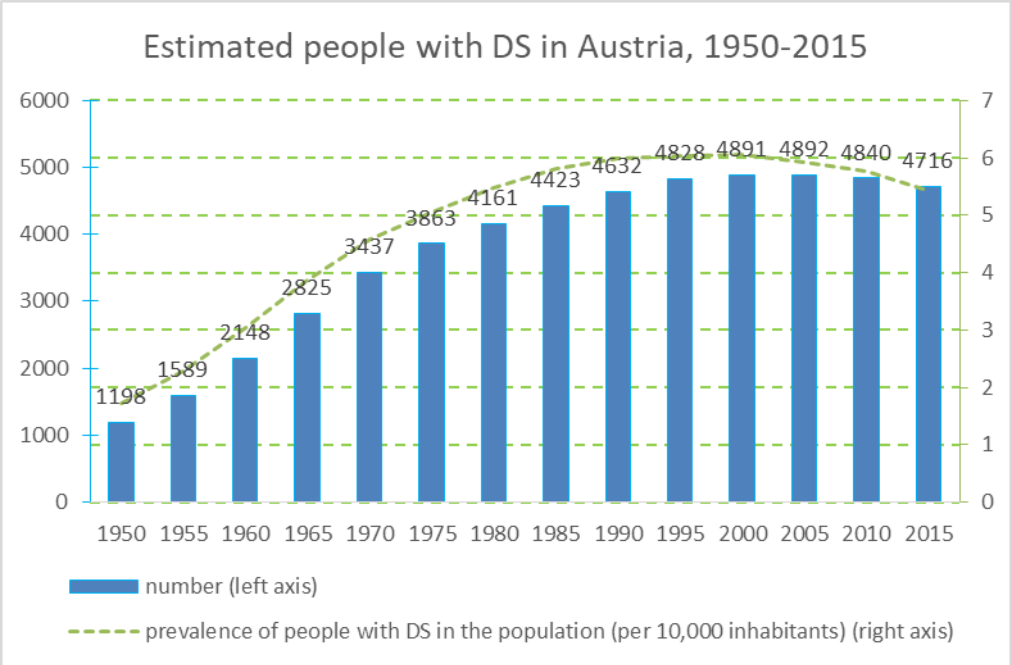


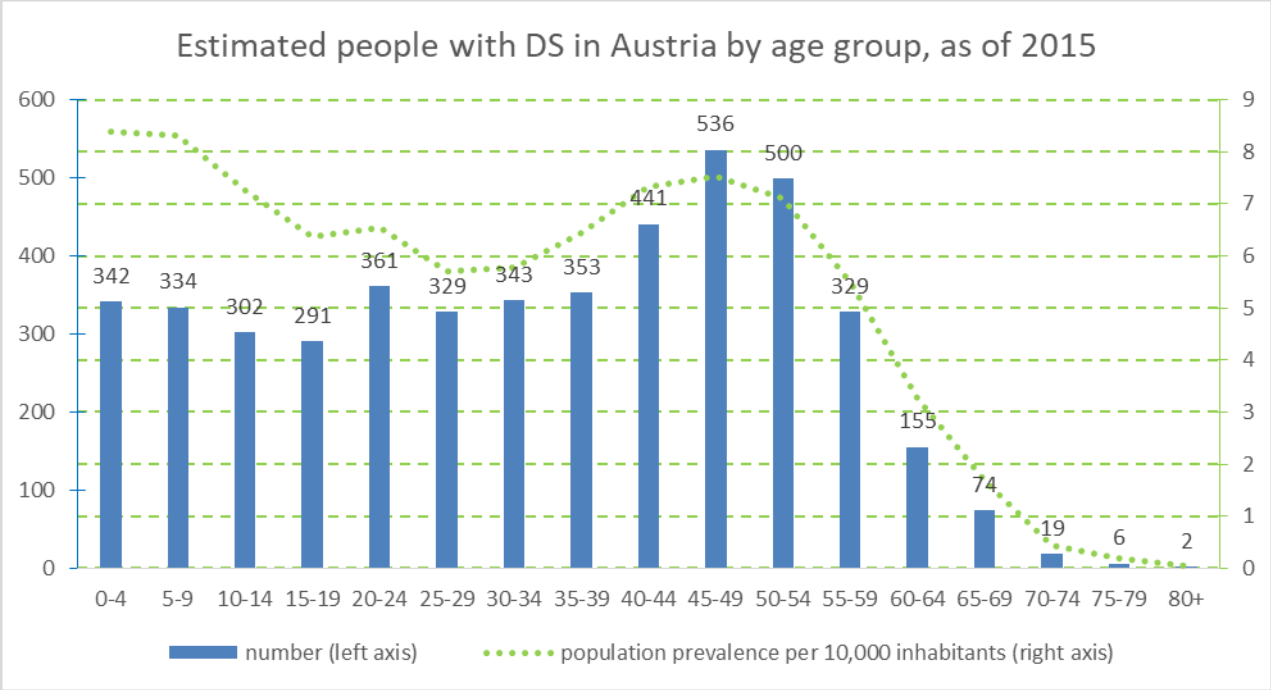




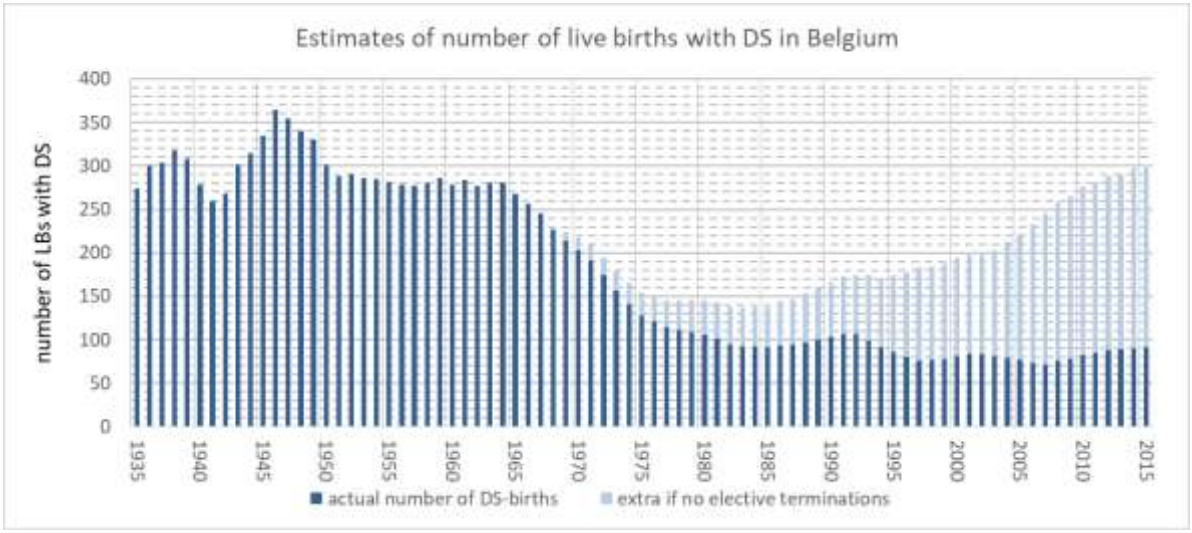

Estimated number of people with DS in Austria by age group, 1950-2015
6000
5000
4000
3000
2000
1000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

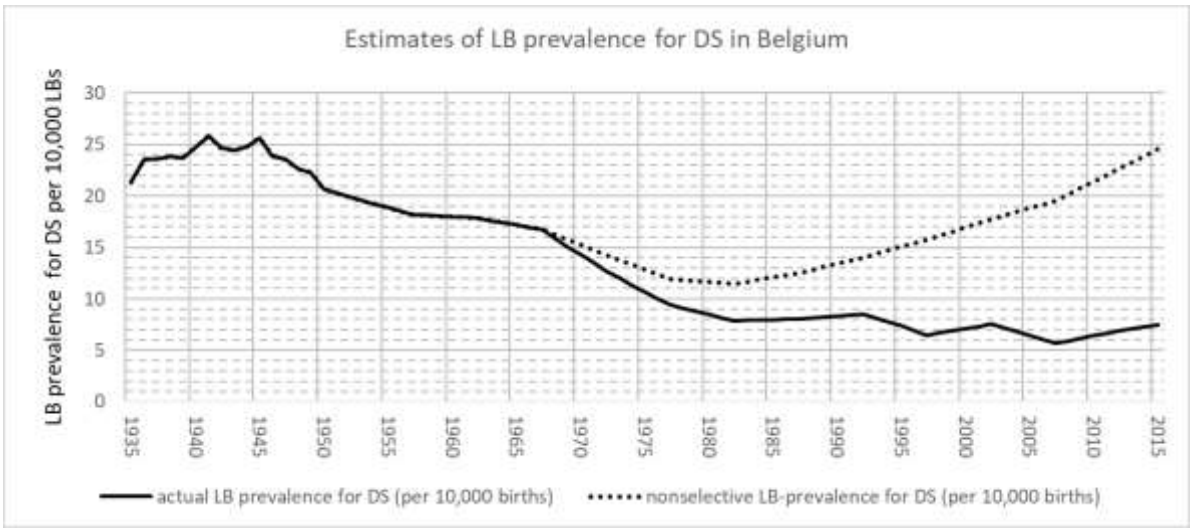

Estimated distribution of people with DS in Austria by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

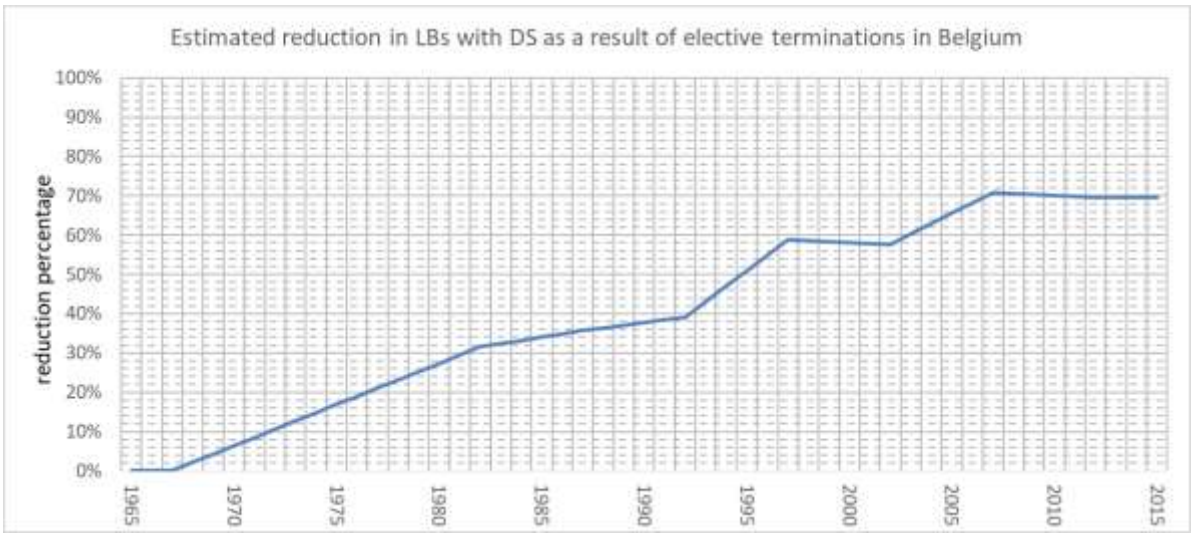

Estimated people with DS in Austria, 1950-2015
6000
5000
4000
3000
2000
1000
0
7
6
5
4
3
2
1
0
1198
1589
2148
2825
3437
3863
4161
4423
4632
4828
4891
4892
4840
4716
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

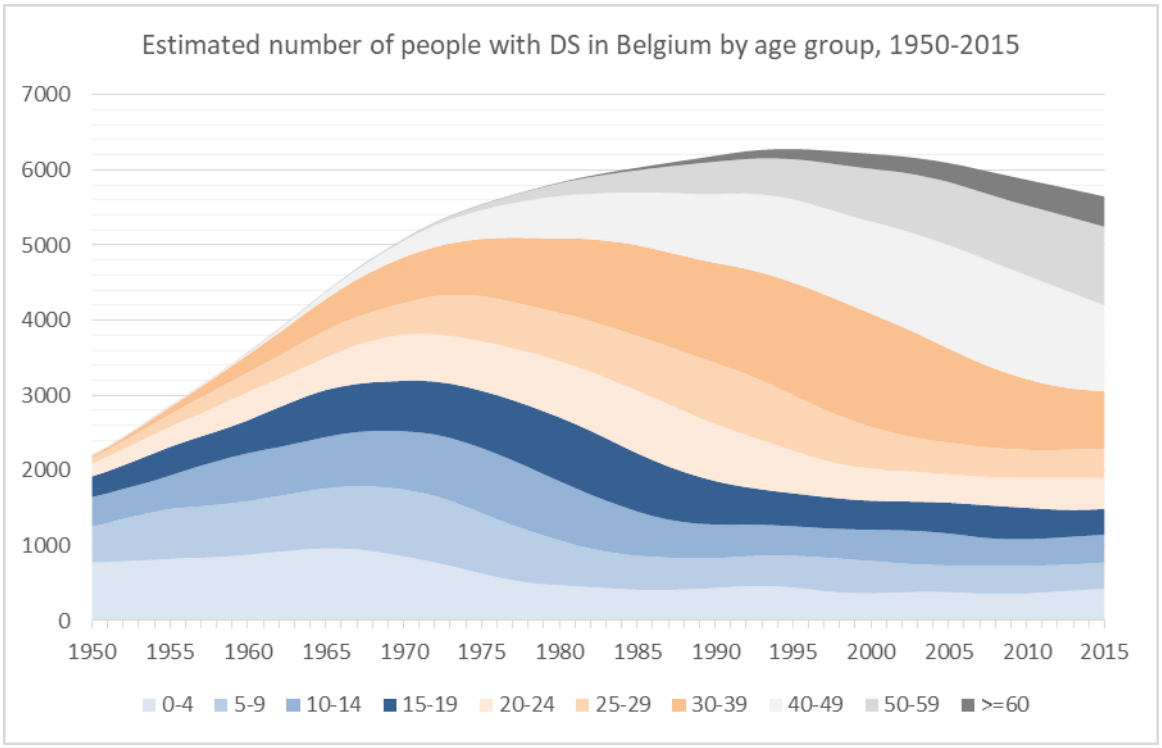

Estimated people with DS in Austria by age group, as of 2015
600
500
400
300
200
100
0
9
8
7
6
5
4
3
2
1
0
342
334
302
291
361
329
343
353
441
536
500
329
155
74
19
6
2
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

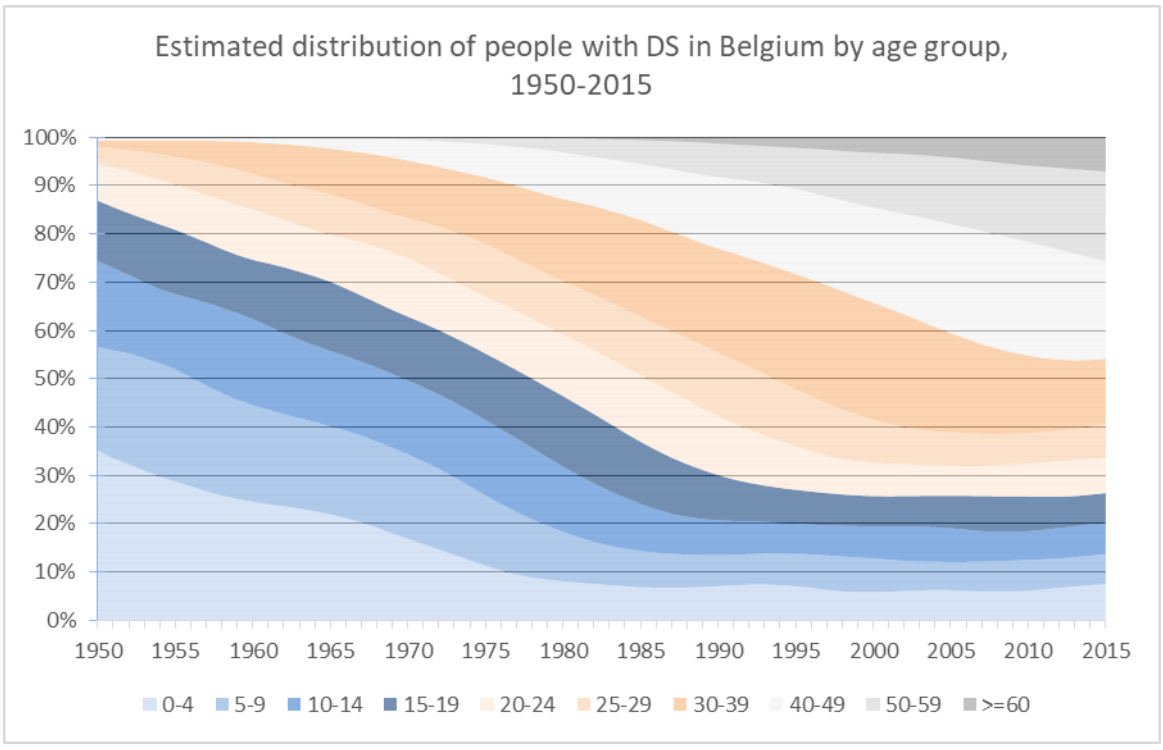
Belgium

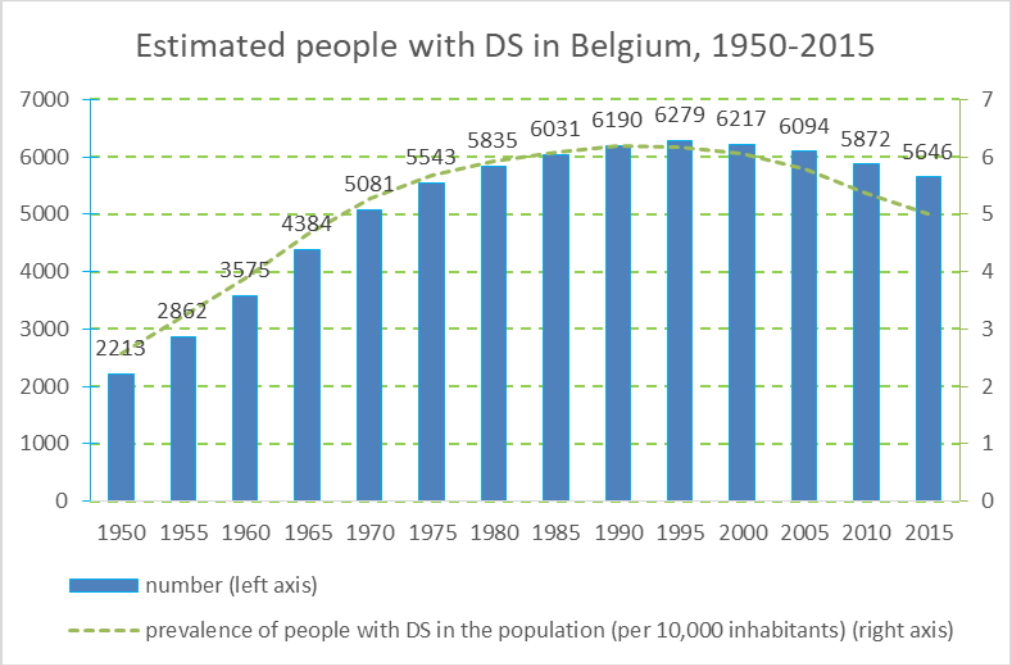

Estimates of number of live births with DS in Belgium
number of LBs with DS
400
350
300
250
200
150
100
50
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

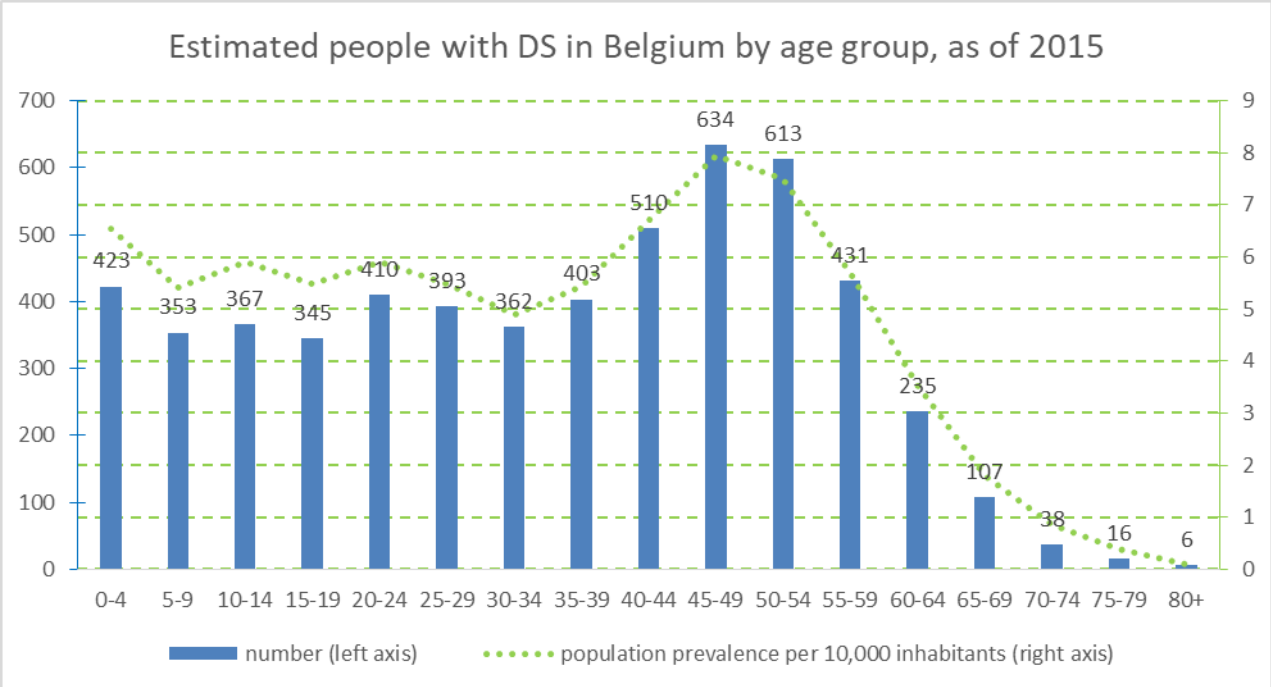

Estimates of LB prevalence for DS in Belgium
LB prevalence for DS per 10,000 LBs
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Belgium
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

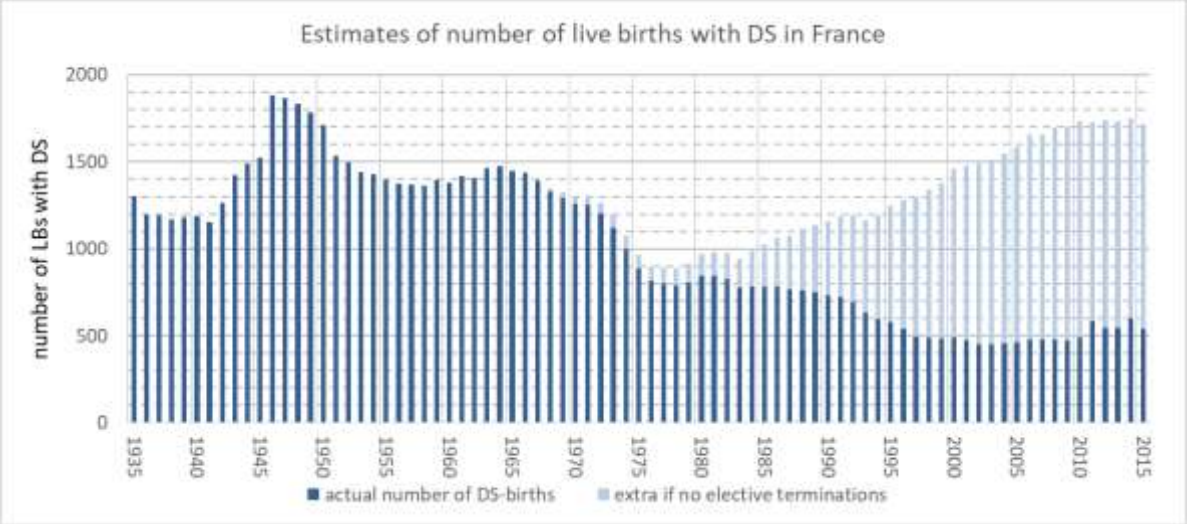

Estimated number of people with DS in Belgium by age group, 1950-2015
7000
6000
5000
4000
3000
2000
1000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

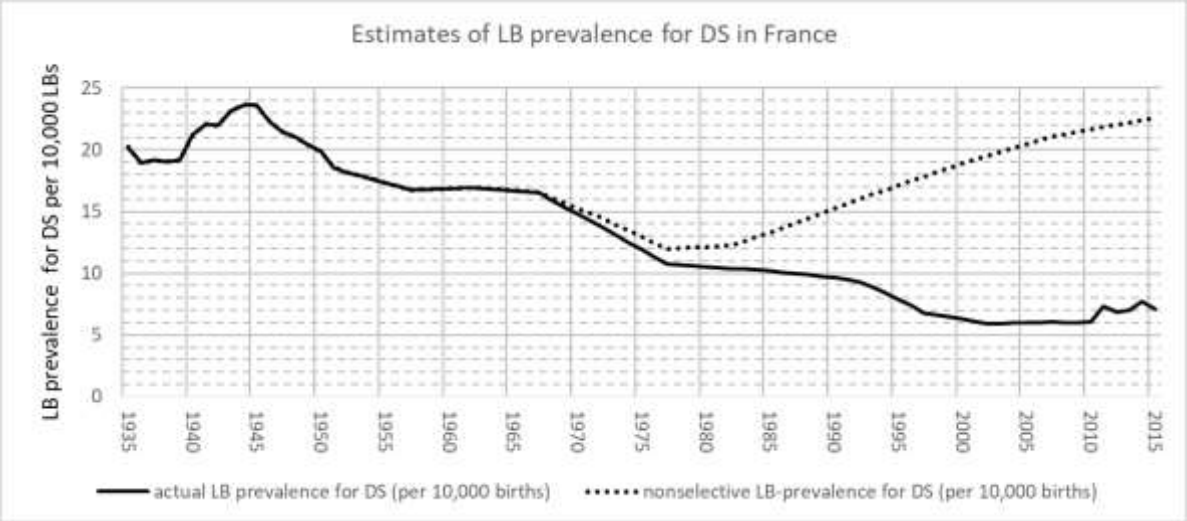

Estimated distribution of people with DS in Belgium by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

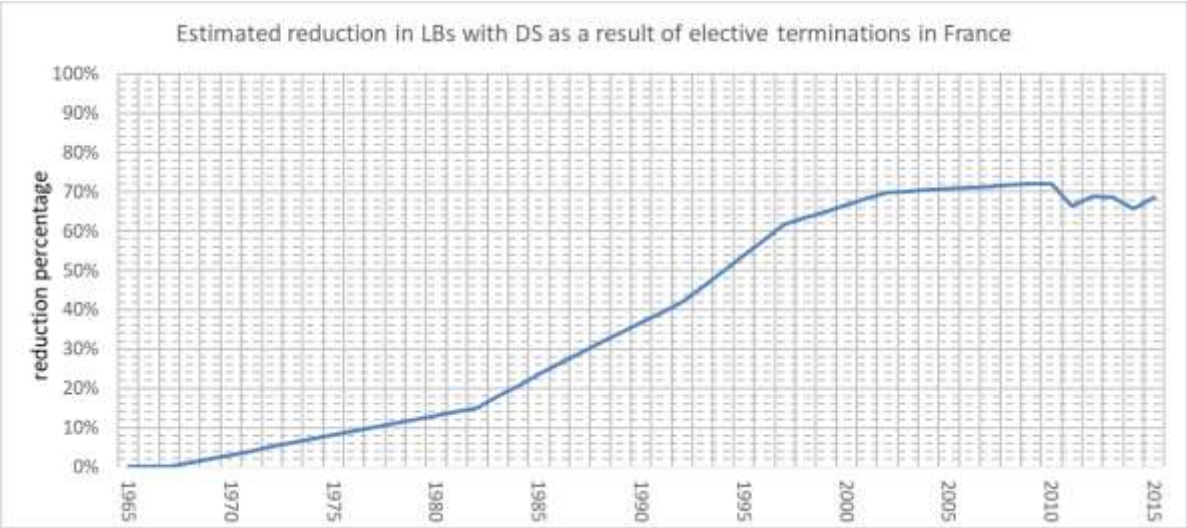

Estimated people with DS in Belgium, 1950-2015
7000
6000
5000
4000
3000
2000
1000
0
7
6
5
4
3
2
1
0
2213
2862
3575
4384
5081
5543
5835
6031
6190
6279
6217
6094
5872
5646
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Belgium by age group, as of 2015
700
600
500
400
300
200
100
0
9
8
7
6
5
4
3
2
1
0
423
353
367
345
410
393
362
403
510
634
613
431
235
107
38
16
6
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

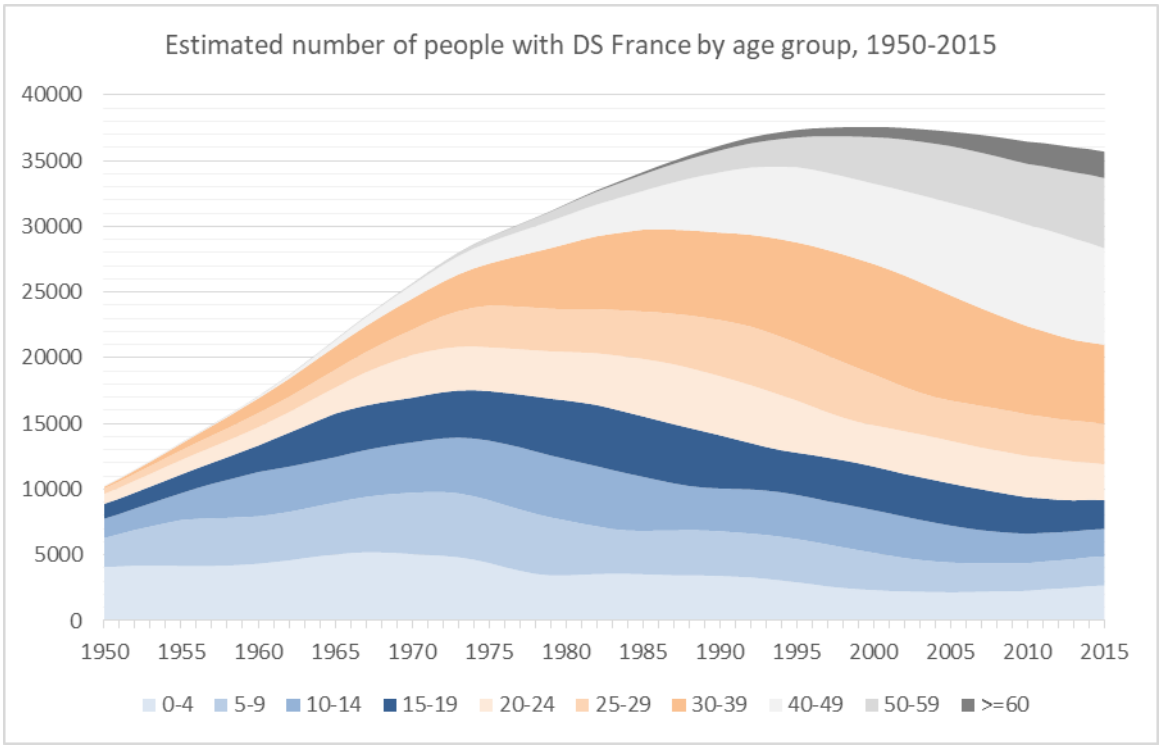
France

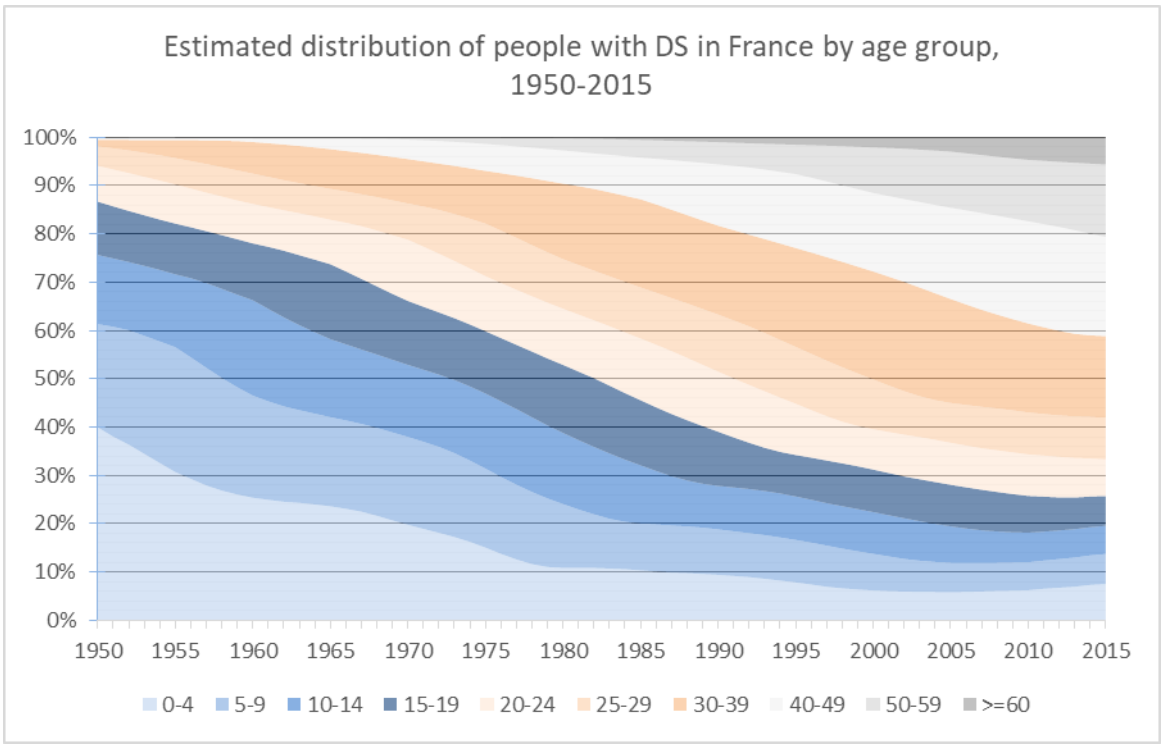


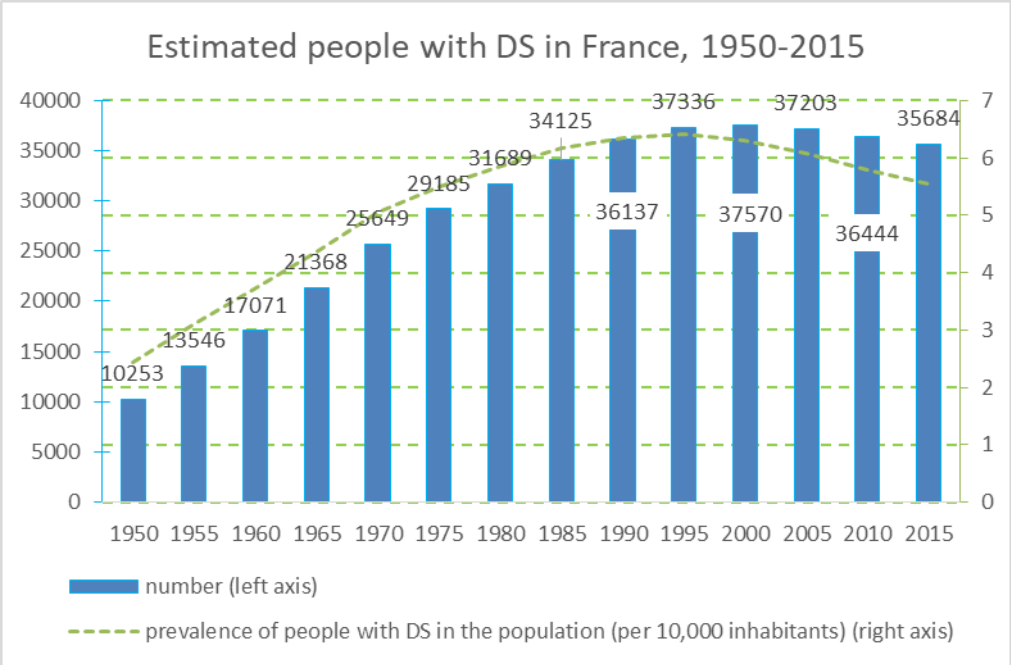


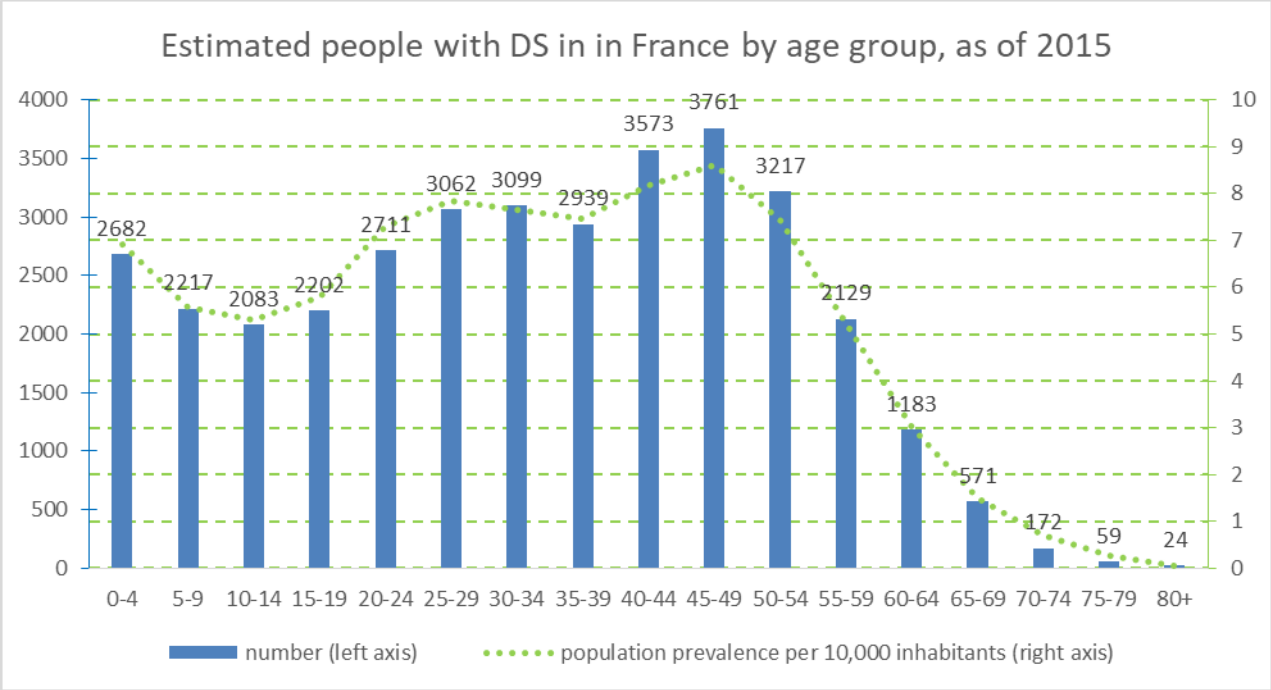


*The lower reduction after 2010 should be interpreted with care. It is not necessarily a change in trend. It might very well be a result of another regional selection, as earlier regional EUROCAT data were used, and after 2010 national data were available.

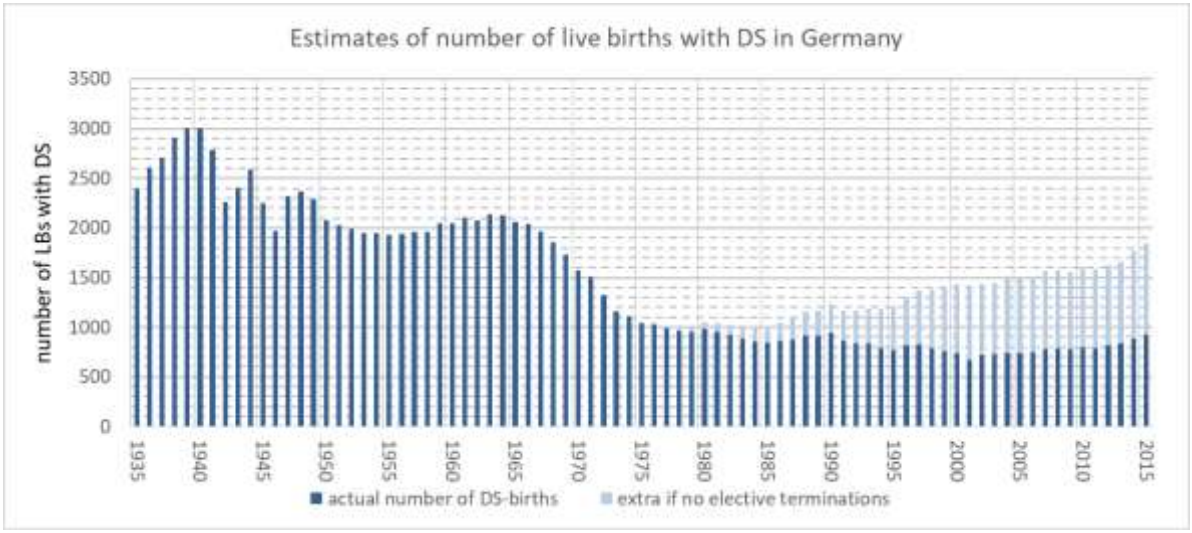

Estimated number of people with DS France by age group, 1950-2015
40000
35000
30000
25000
20000
15000
10000
5000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

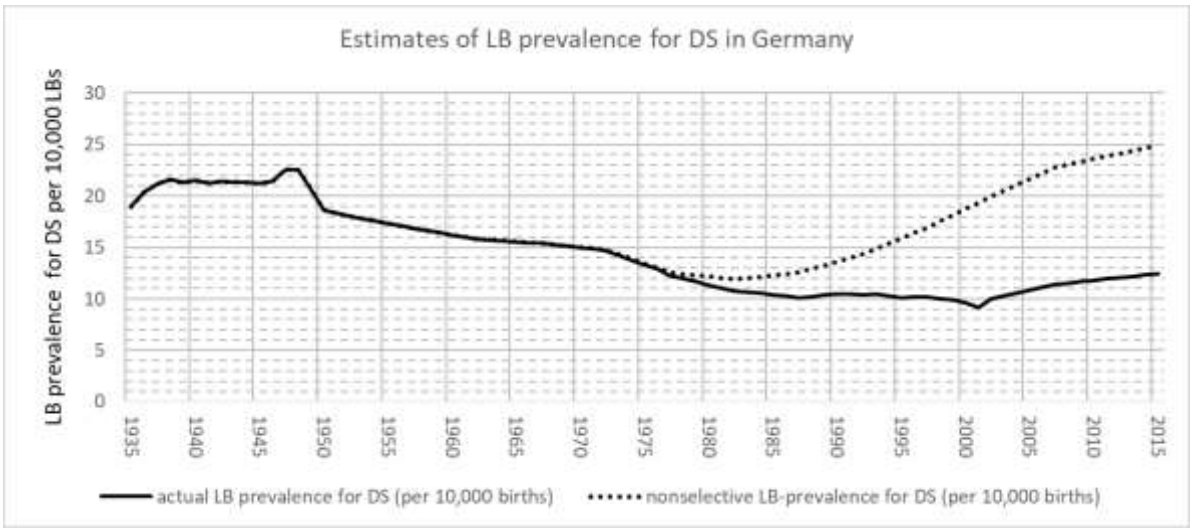

Estimated distribution of people with DS in France by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

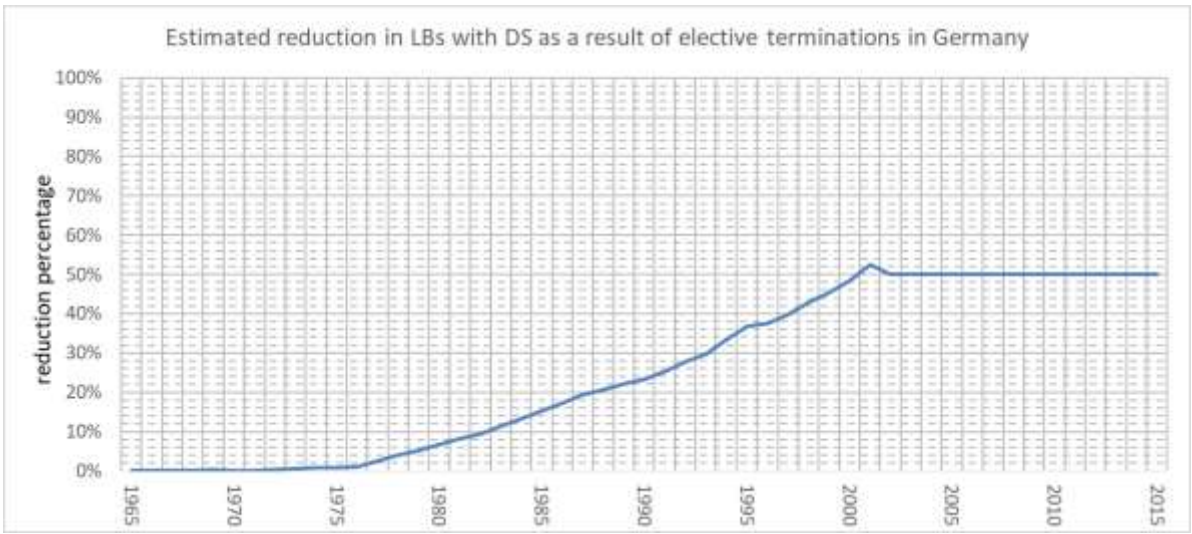

Estimated people with DS in France, 1950-2015
40000
35000
30000
25000
20000
15000
10000
5000
0
7
6
5
4
3
2
1
0
10253
13546
17071
21368
25649
29185
31689
34125
36137
37336
37570
37203
36444
35684
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

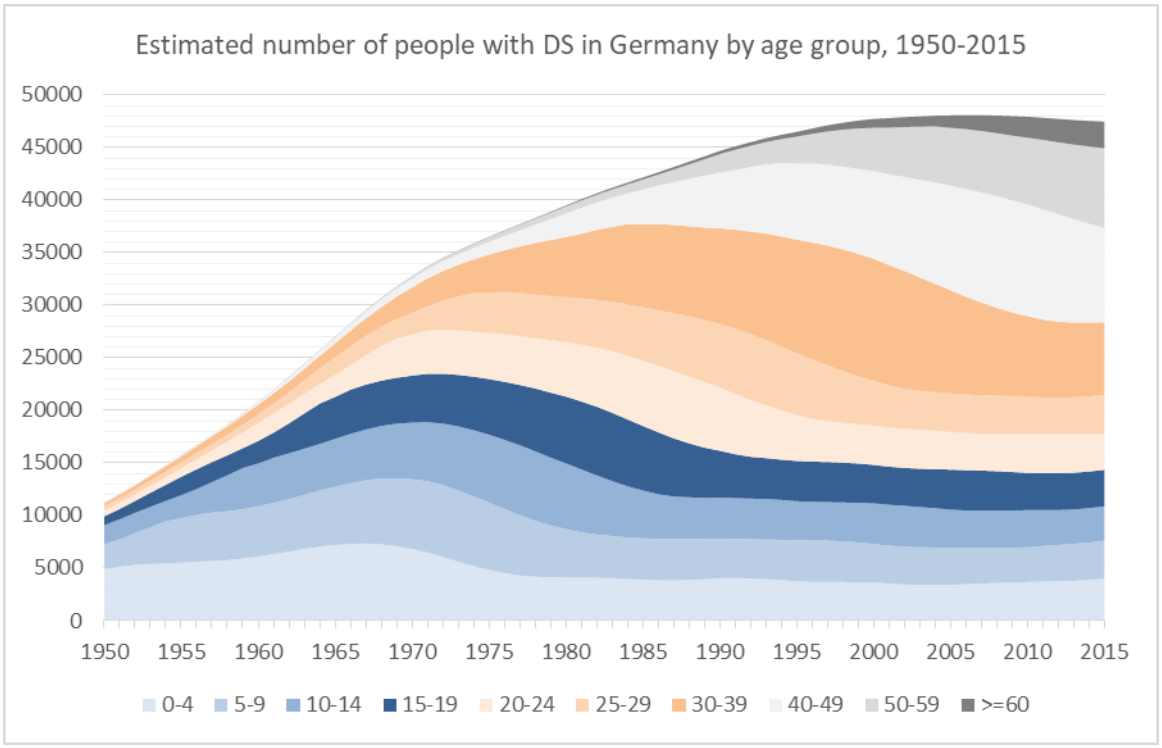

Estimated people with DS in in France by age group, as of 2015
4000
3500
3000
2500
2000
1500
1000
500
0
10
9
8
7
6
5
4
3
2
1
0
2682
2217
2083
2202
2711
3062
3099
2939
3573
3761
3217
2129
1183
571
172
59
24
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

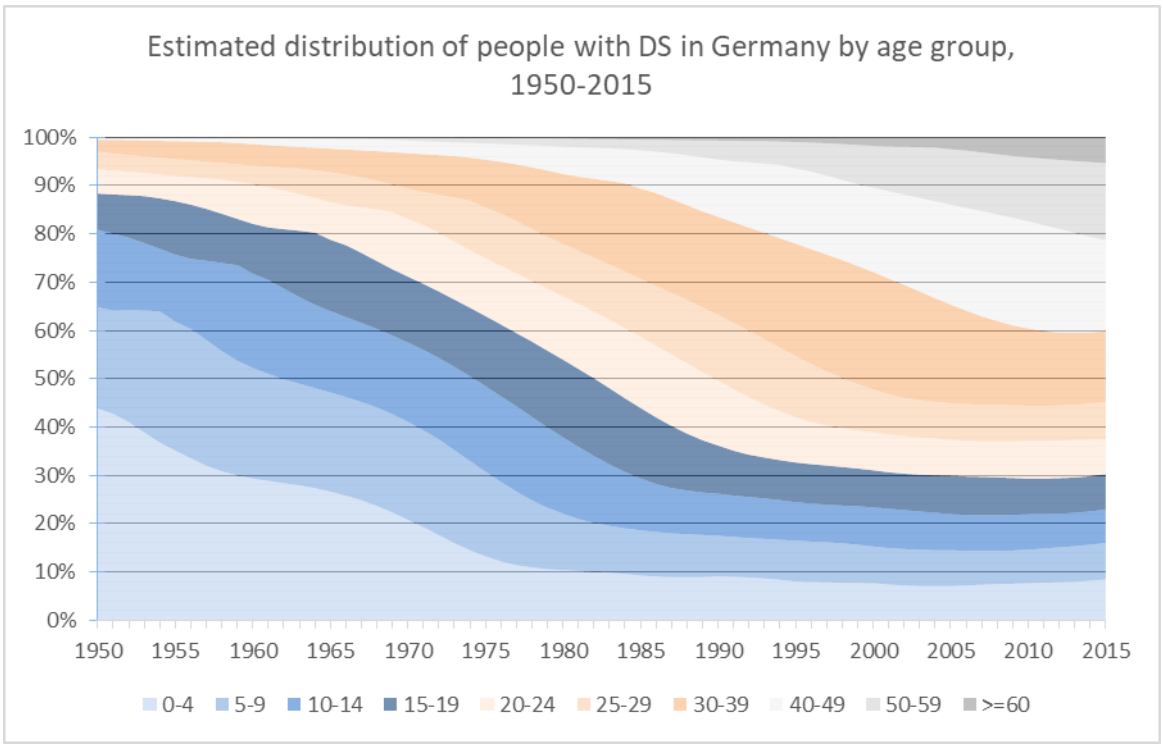
Germany

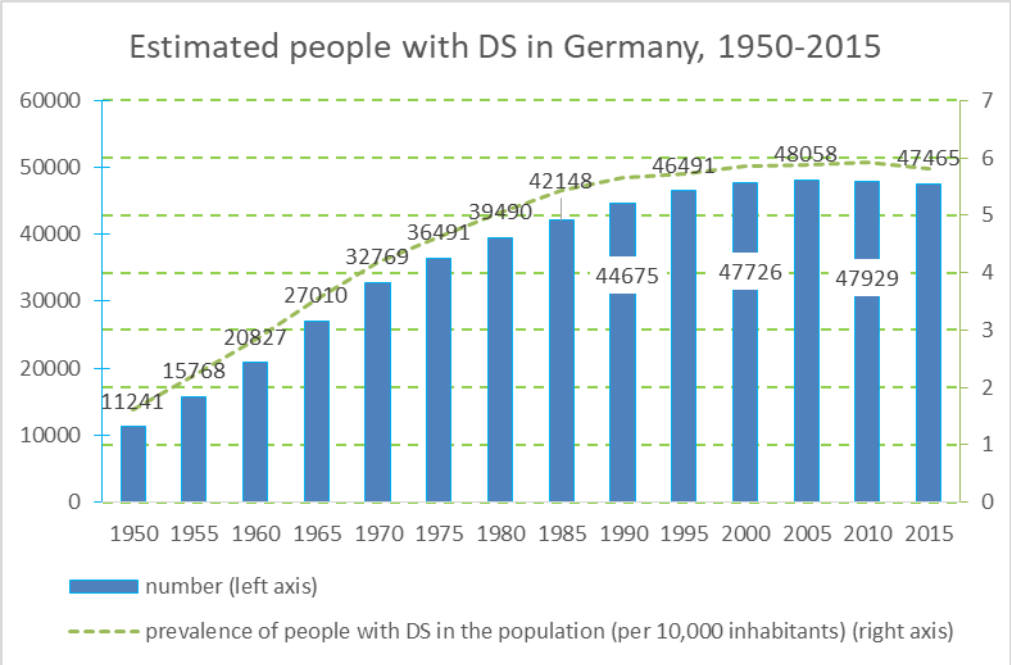

Estimates of number of live births with DS in Germany
number of LBs with DS
3500
3000
2500
2000
1500
1000
500
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

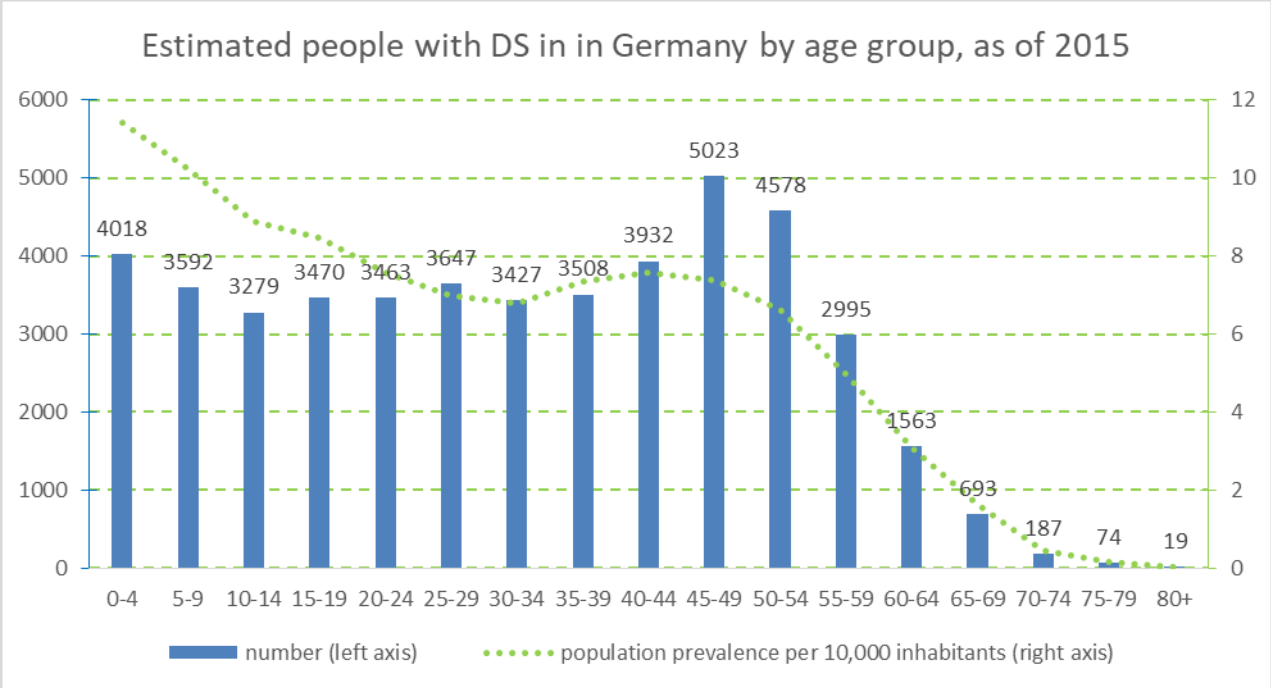

Estimates of LB prevalence for DS in Germany
LB prevalence for DS per 10,000 LBs
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Germany
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

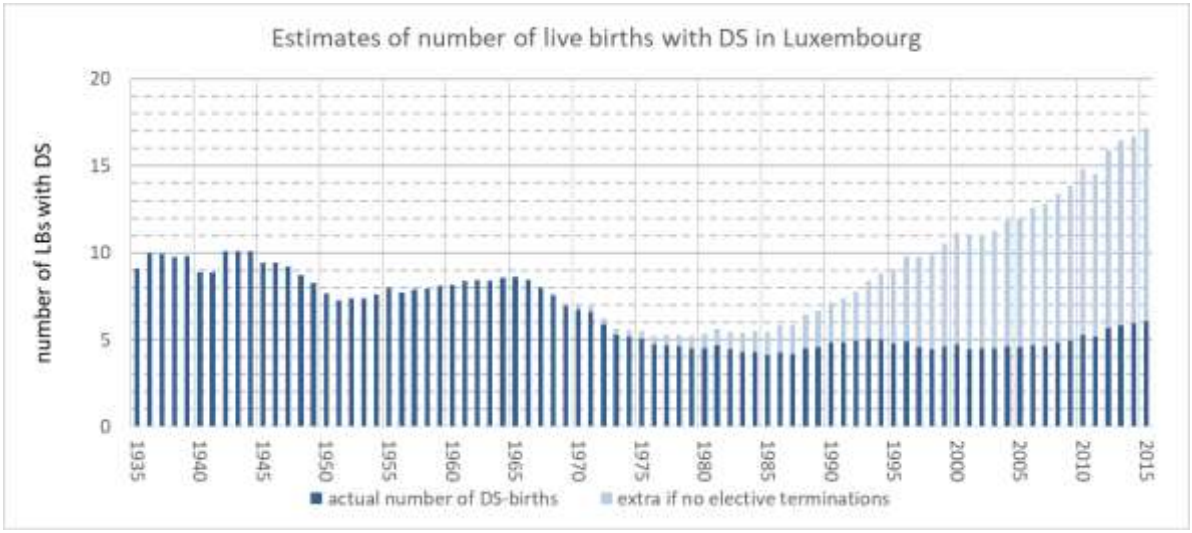

Estimated number of people with DS in Germany by age group, 1950-2015
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

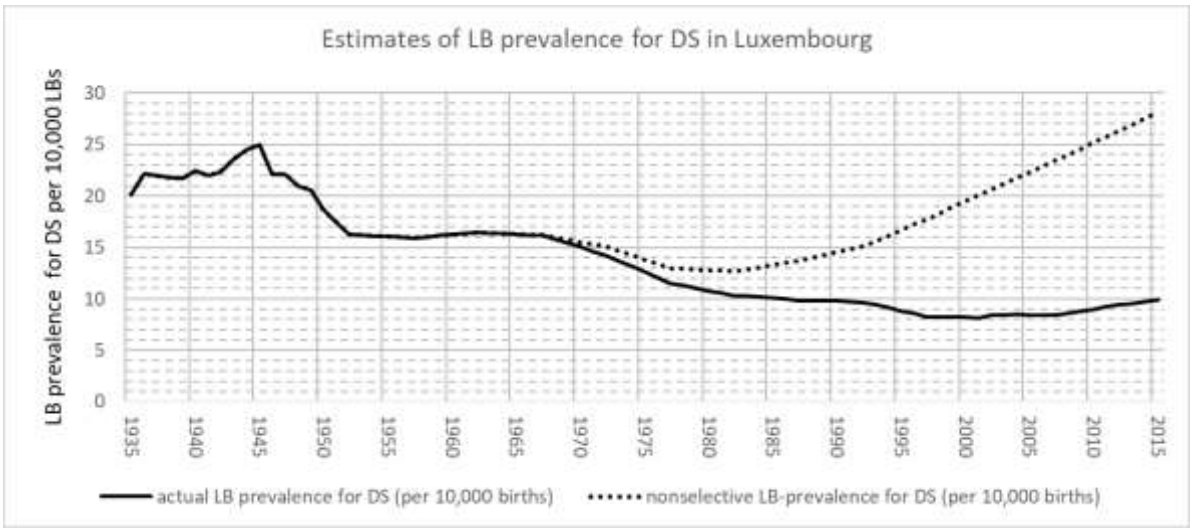

Estimated distribution of people with DS in Germany by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

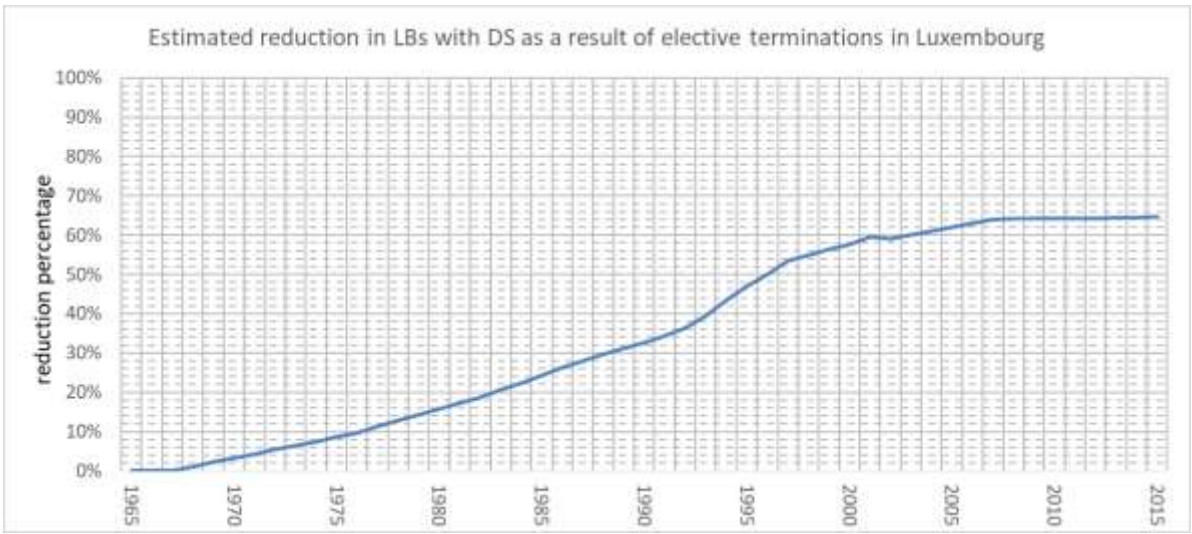

Estimated people with DS in Germany, 1950-2015
60000
50000
40000
30000
20000
10000
0
7
6
5
4
3
2
1
0
11241
15768
20827
27010
32769
36491
39490
42148
44675
46491
47726
48058
47929
47465
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

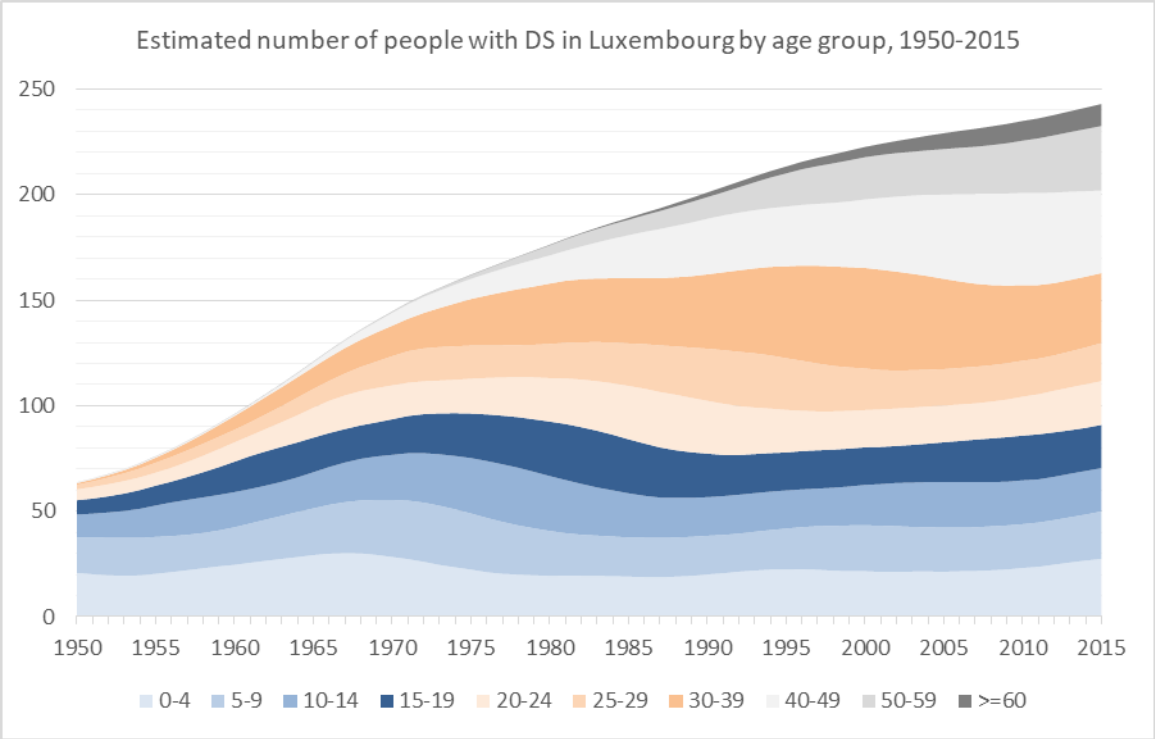

Estimated people with DS in in Germany by age group, as of 2015
6000
5000
4000
3000
2000
1000
0
12
10
8
6
4
2
0
4018
3592
3279
3470
3463
3647
3427
3508
3932
5023
4578
2995
1563
693
187
74
19
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

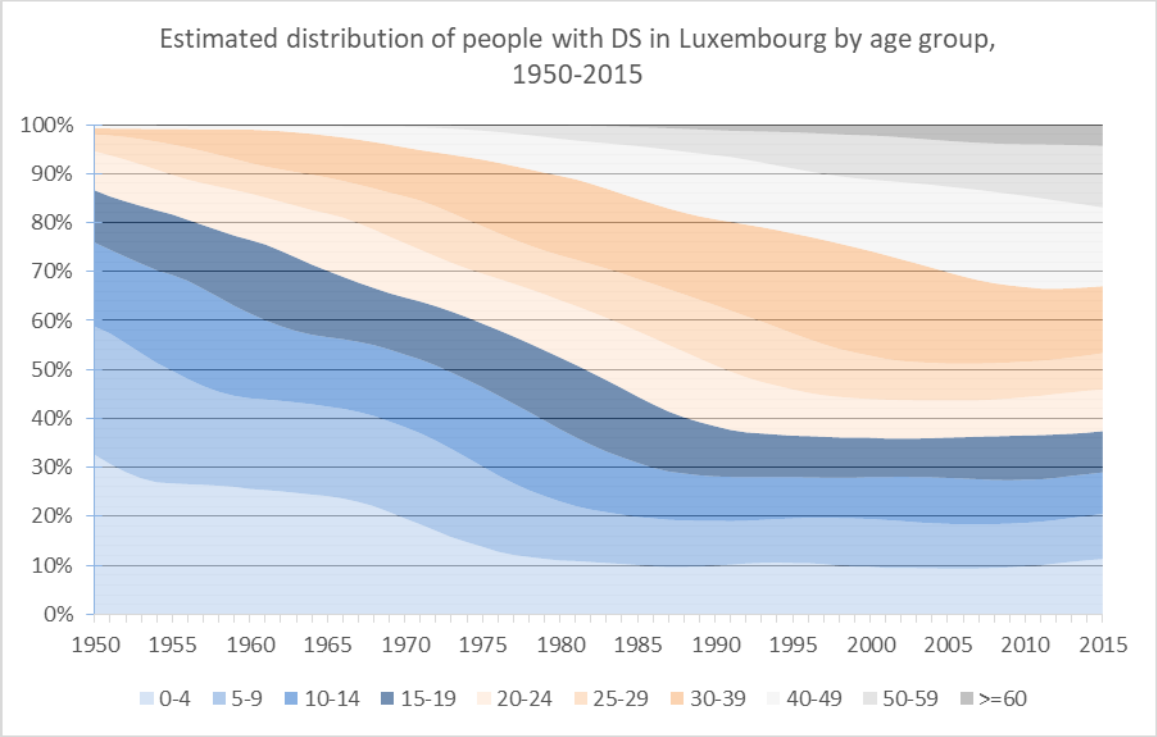
Luxembourg

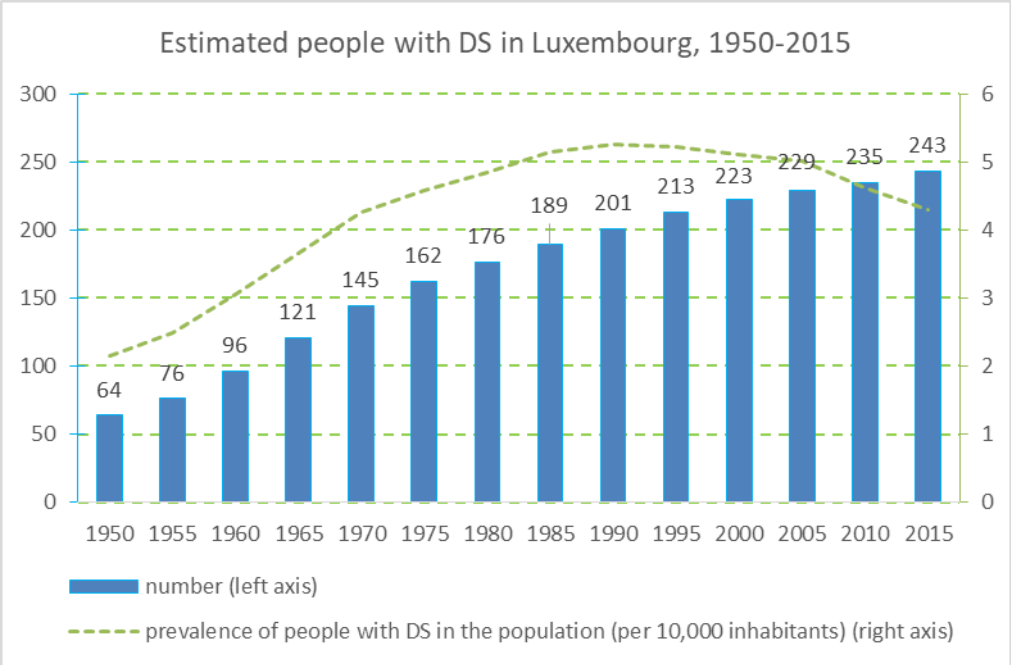

Estimates of number of live births with DS in Luxembourg
number of LBs with DS
0
5
10
15
20
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

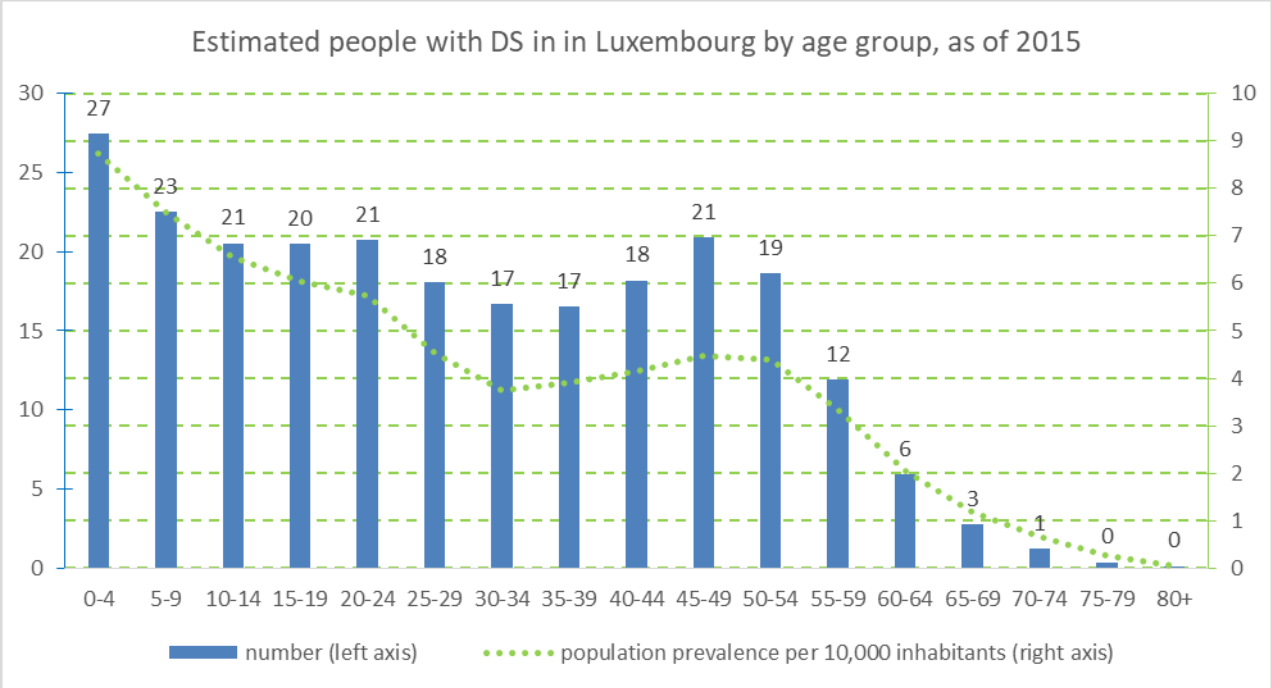

Estimates of LB prevalence for DS in Luxembourg
LB prevalence for DS per 10,000 LBs
0
5
10
15
20
25
30
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Luxembourg
reduction percentage
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

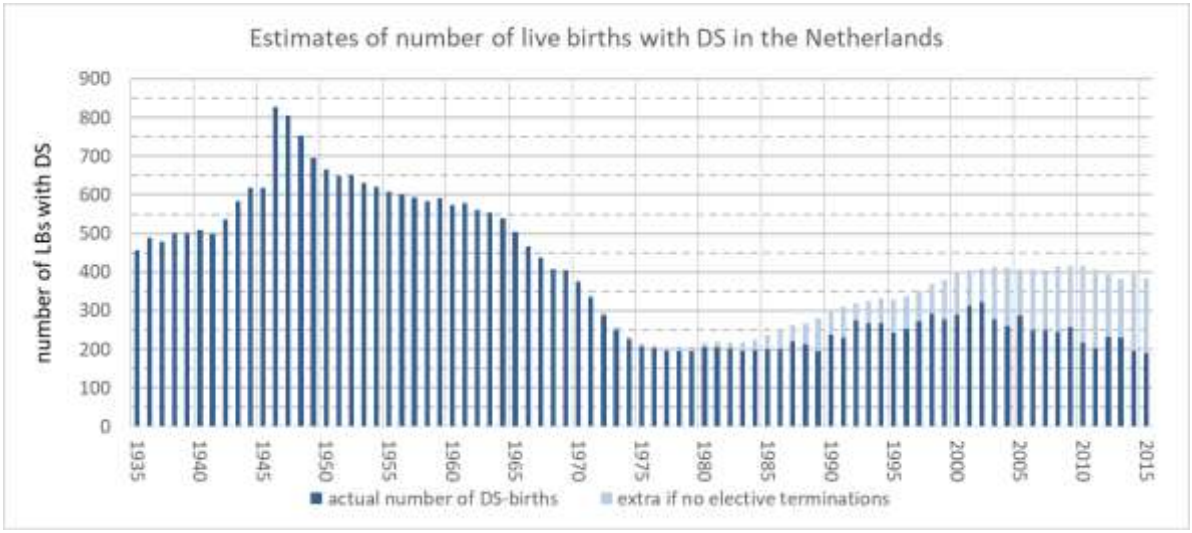

Estimated number of people with DS in Luxembourg by age group, 1950-2015
250
200
150
100
50
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

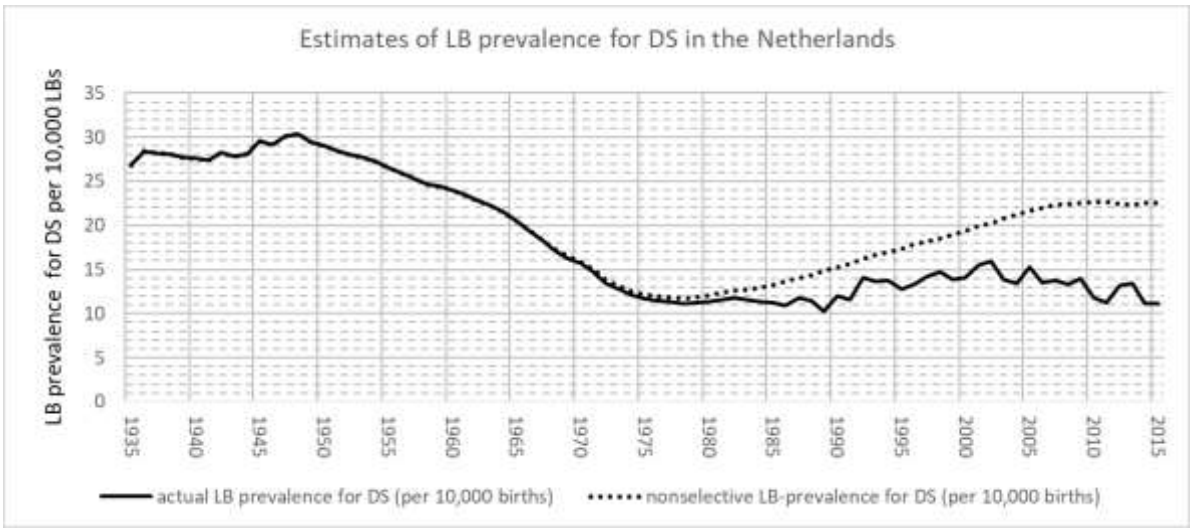

Estimated distribution of people with DS in Luxembourg by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

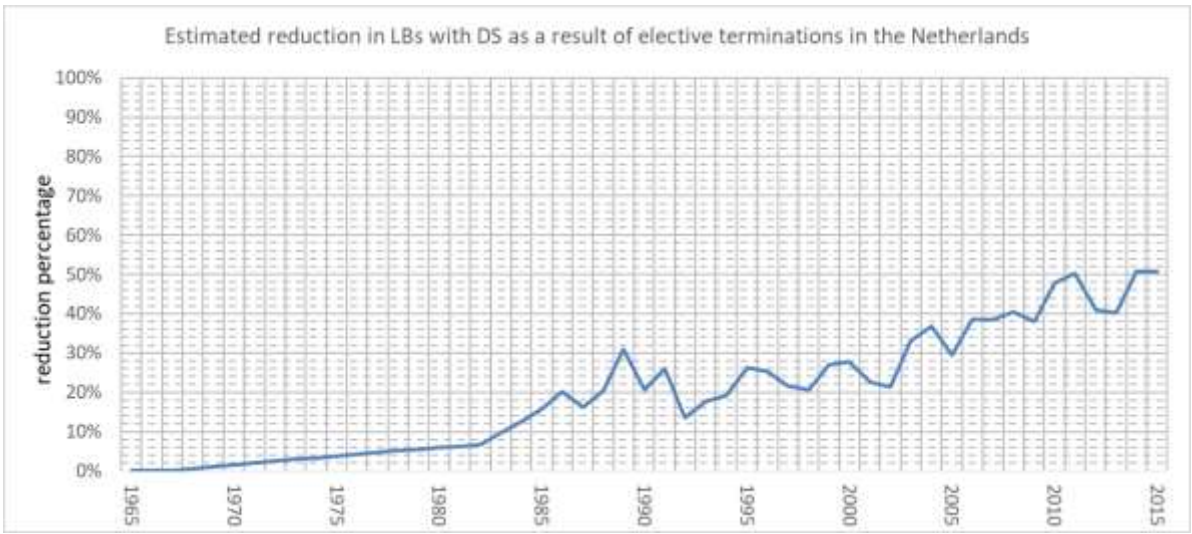

Estimated people with DS in Luxembourg, 1950-2015
300
250
200
150
100
50
0
6
5
4
3
2
1
0
64
76
96
121
145
162
176
189
201
213
223
229
235
243
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

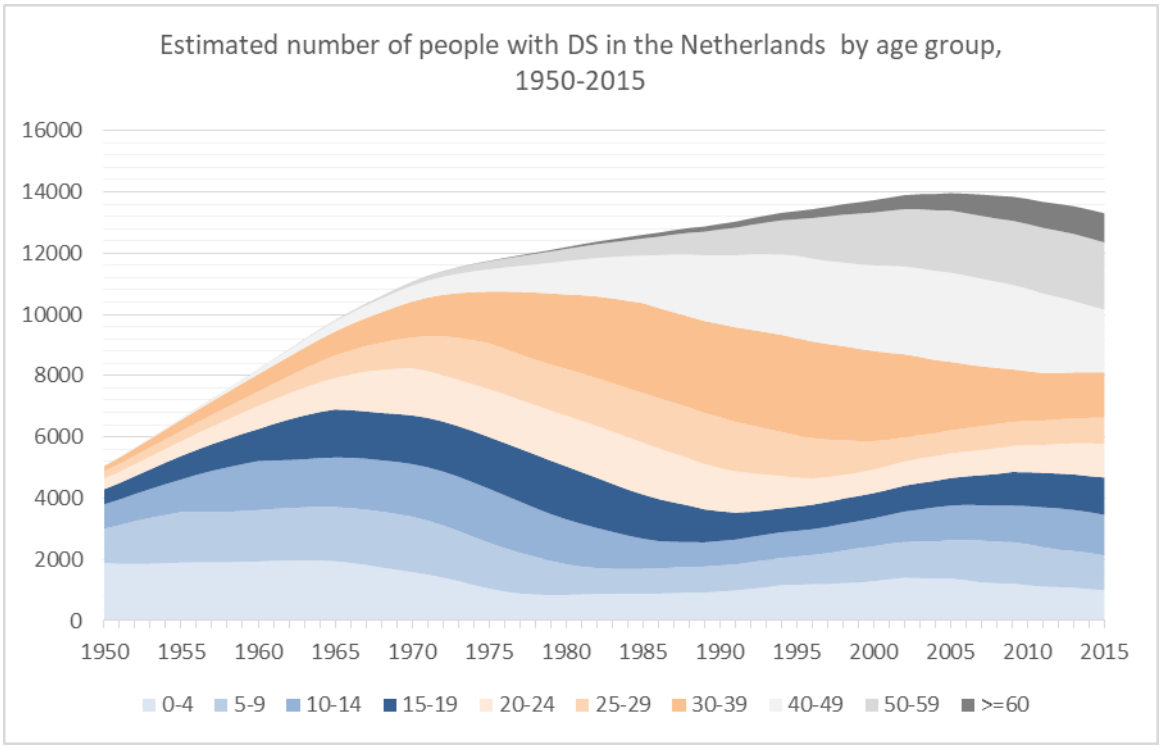

Estimated people with DS in in Luxembourg by age group, as of 2015
30
25
20
15
10
5
0
10
9
8
7
6
5
4
3
2
1
0
27
23
21
20
21
18
17
17
18
21
19
12
6
3
1
0
0
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

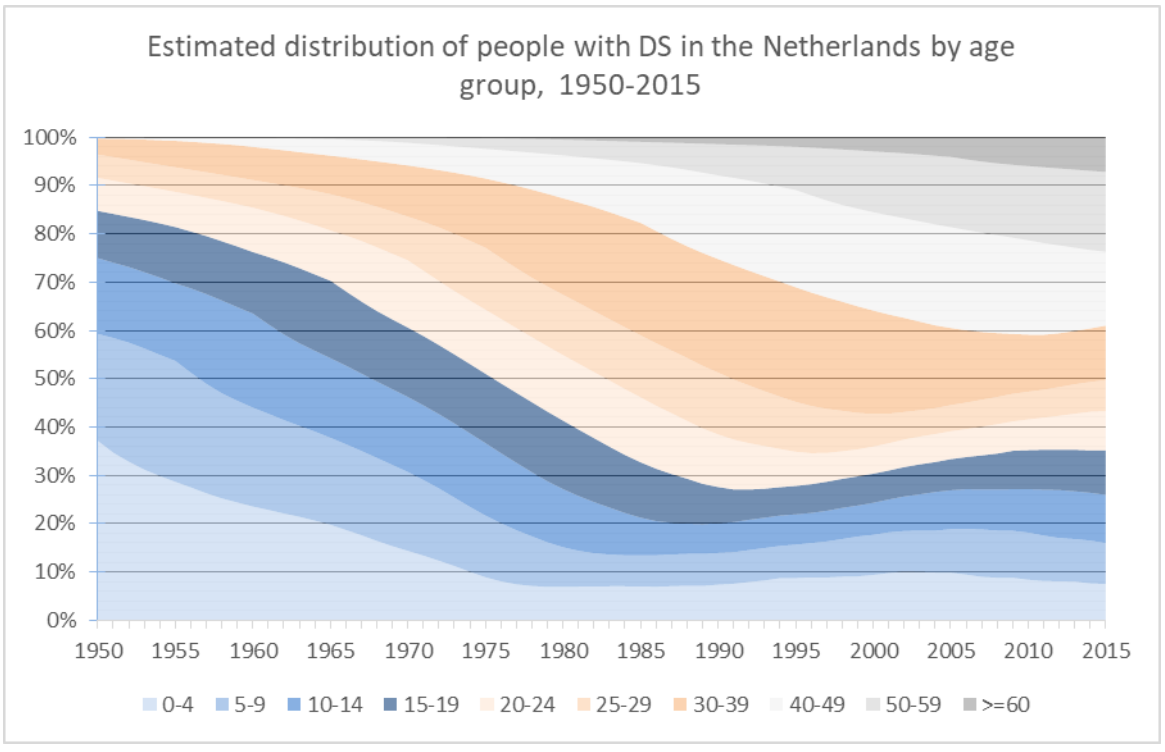
Netherlands

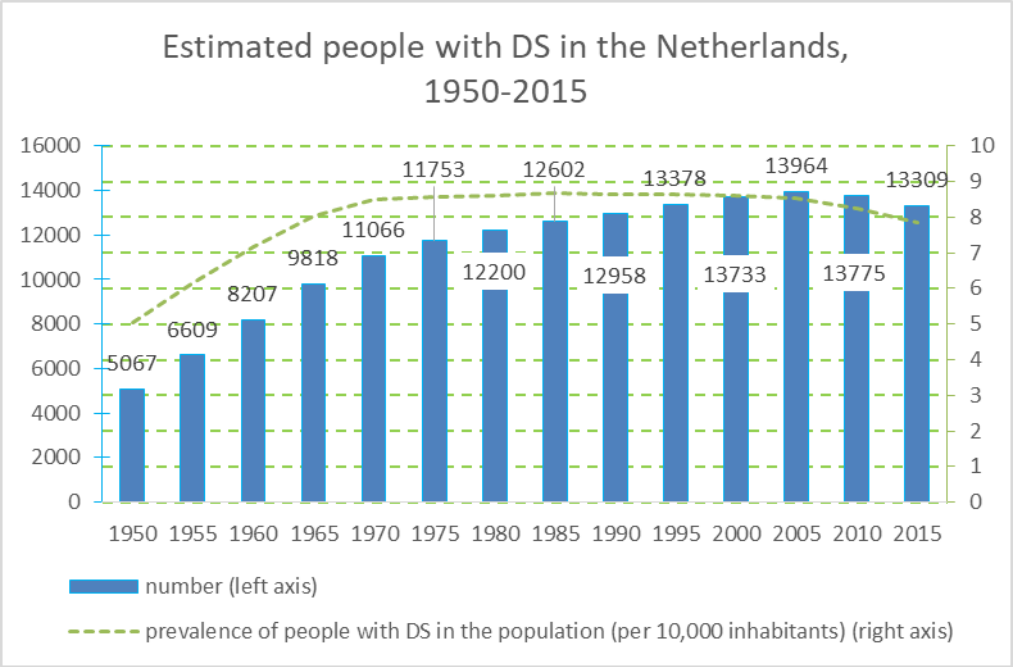


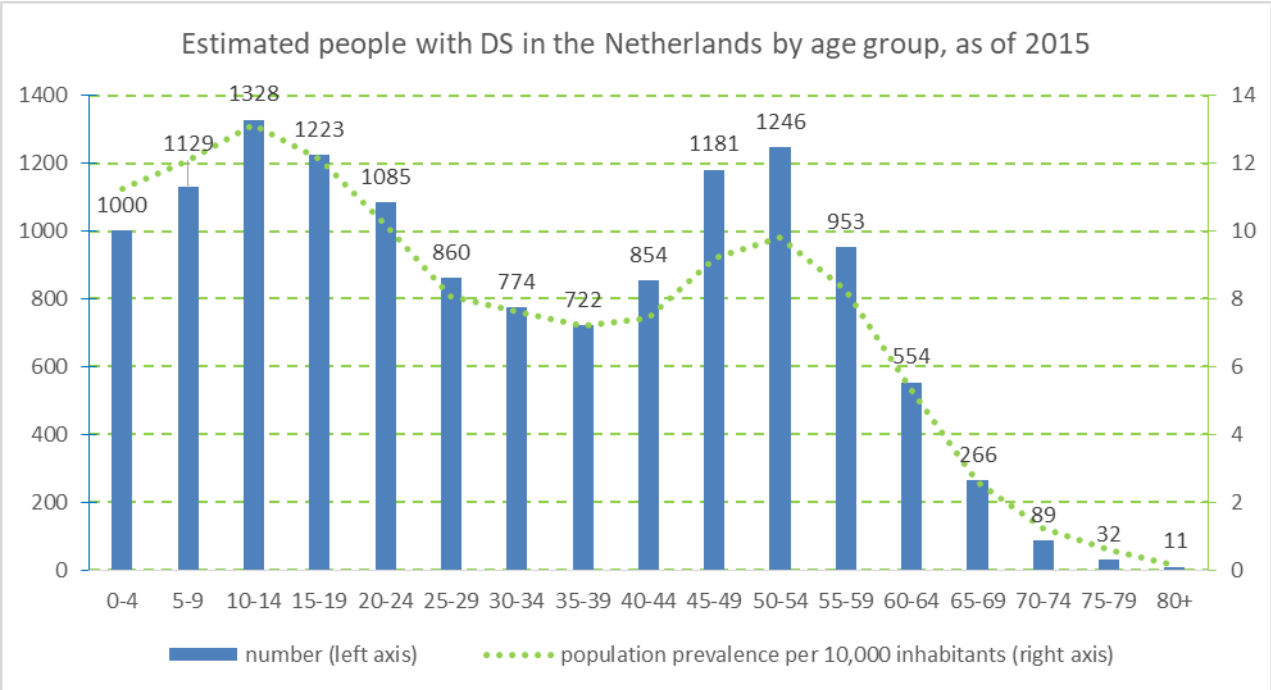




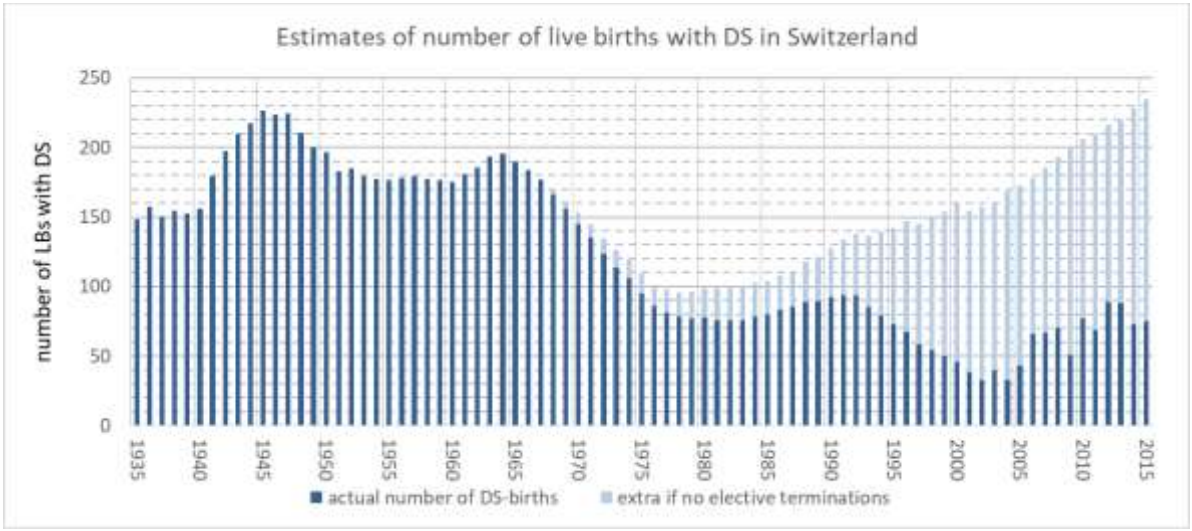

Estimated number of people with DS in the Netherlands by age group, 1950-2015
16000
14000
12000
10000
8000
6000
4000
2000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

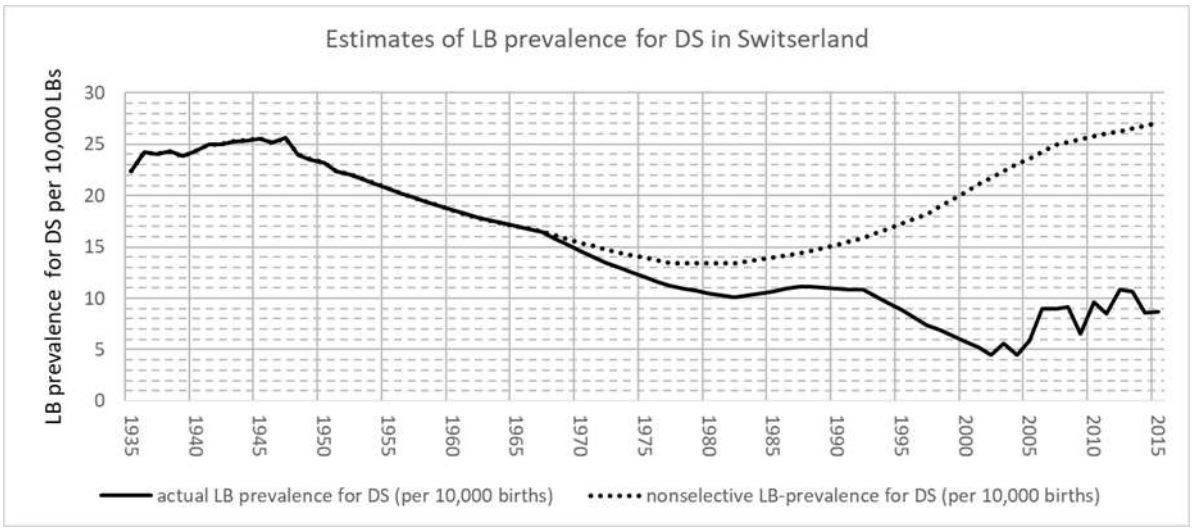

Estimated distribution of people with DS in the Netherlands by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

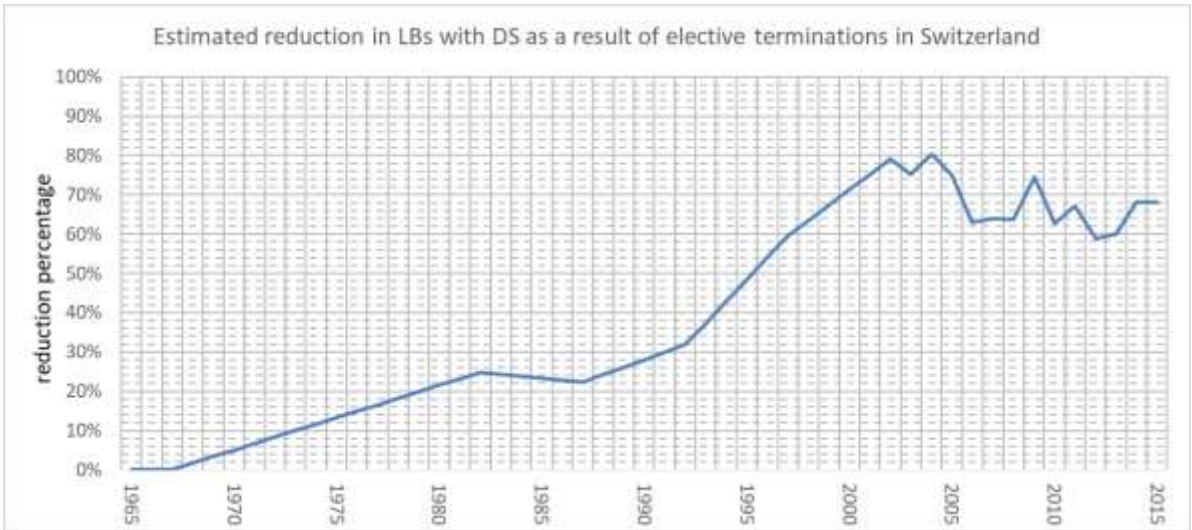

Estimated people with DS in the Netherlands, 1950-2015
16000
14000
12000
10000
8000
6000
4000
2000
0
10
9
8
7
6
5
4
3
2
1
0
5067
6609
8207
9818
11066
11753
12200
12602
12958
13378
13733
13964
13775
13309
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

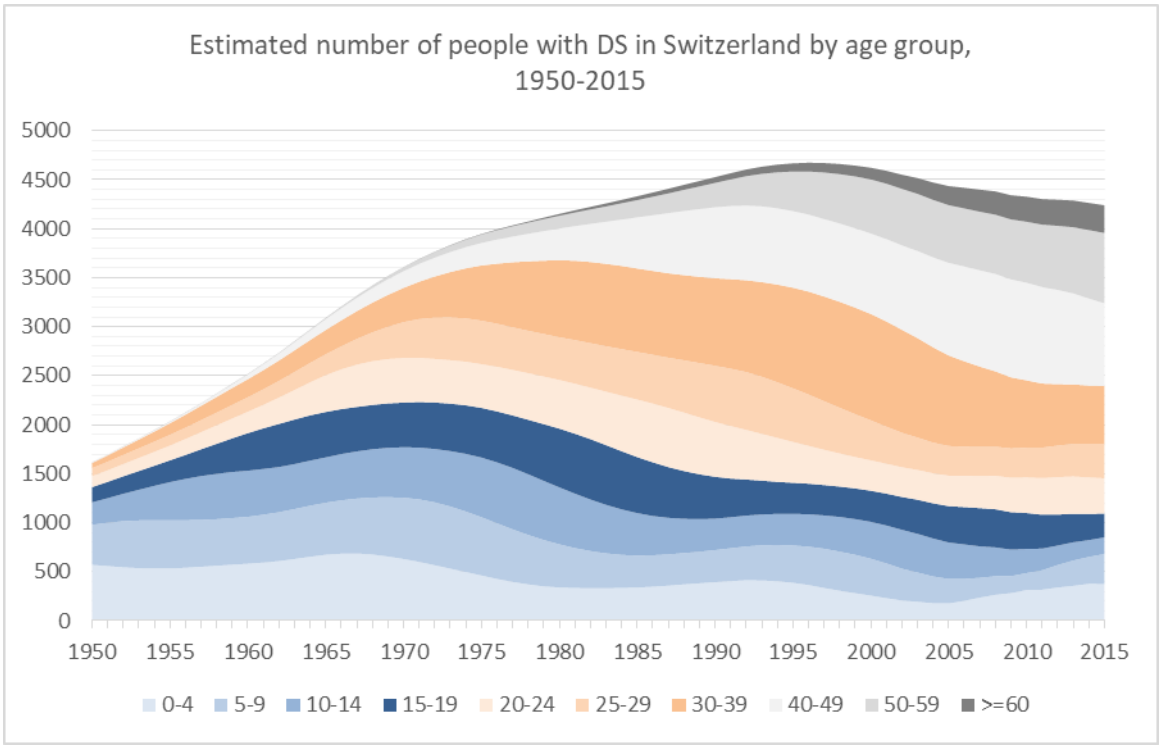

Estimated people with DS in the Netherlands by age group, as of 2015
1400
1200
1000
800
600
400
200
0
14
12
10
8
6
4
2
0
1000
1129
1328
1223
1085
860
774
722
854
1181
1246
953
554
266
89
32
11
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

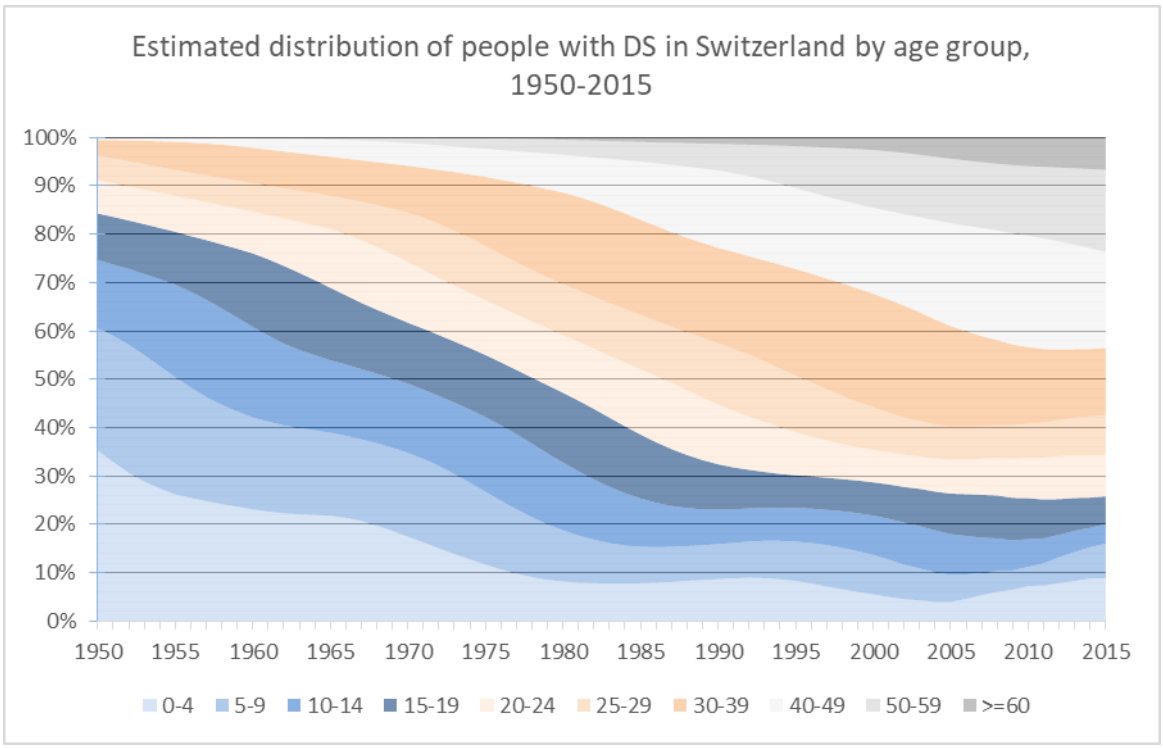
Switzerland

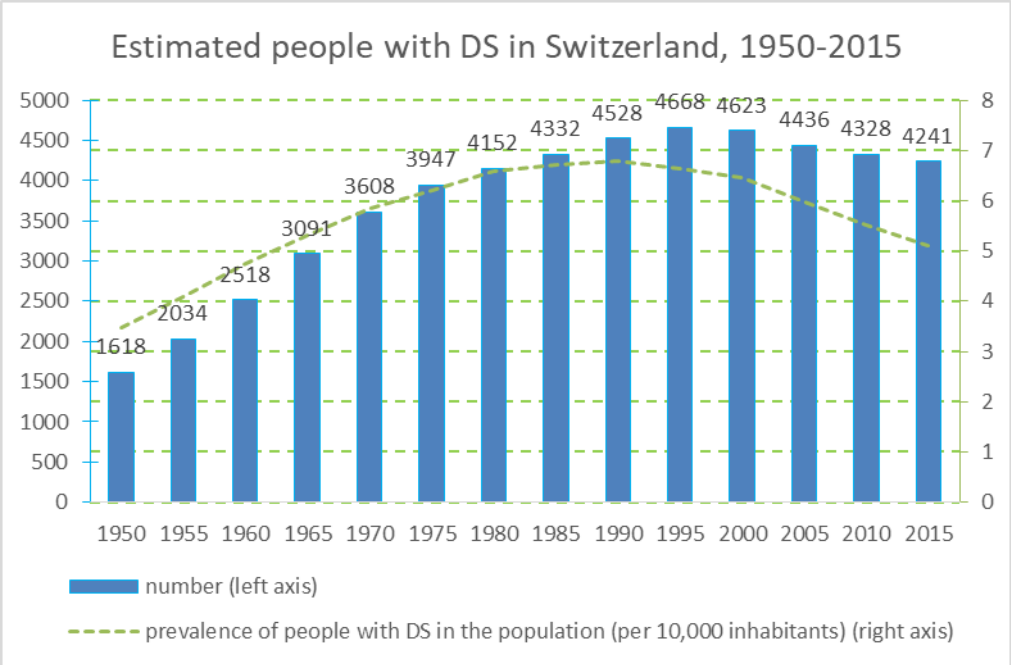


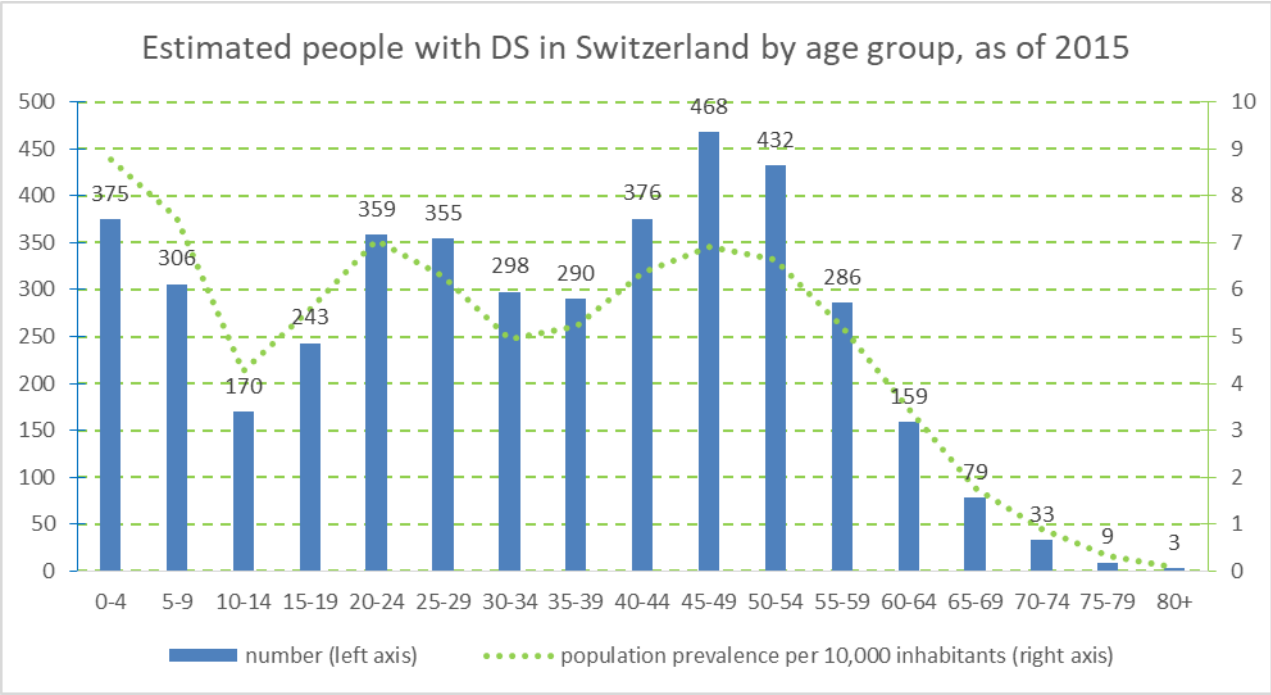





Estimated number of people with DS in Switzerland by age group, 1950-2015
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

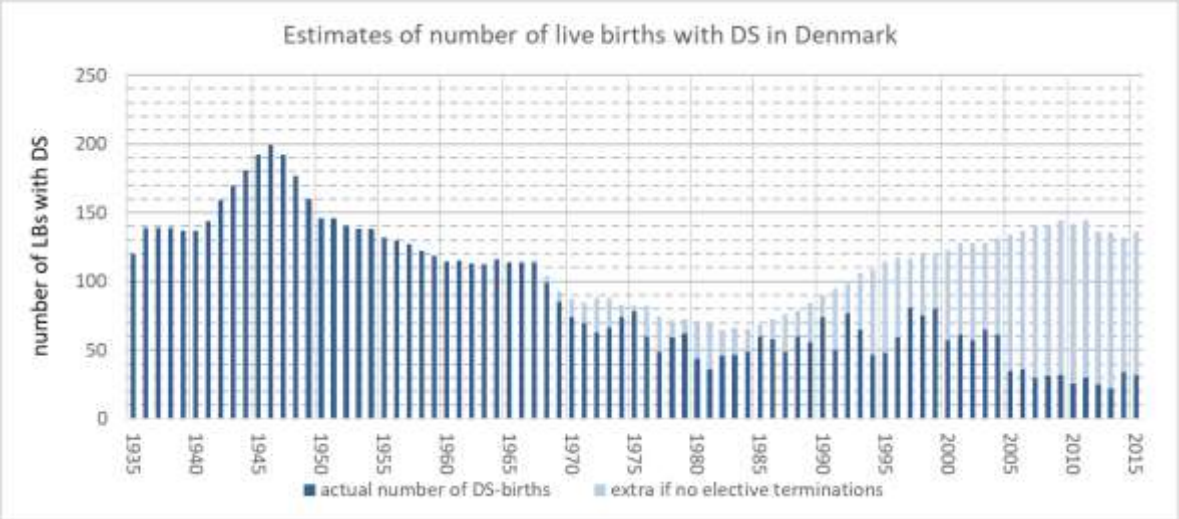

Estimated distribution of people with DS in Switzerland by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

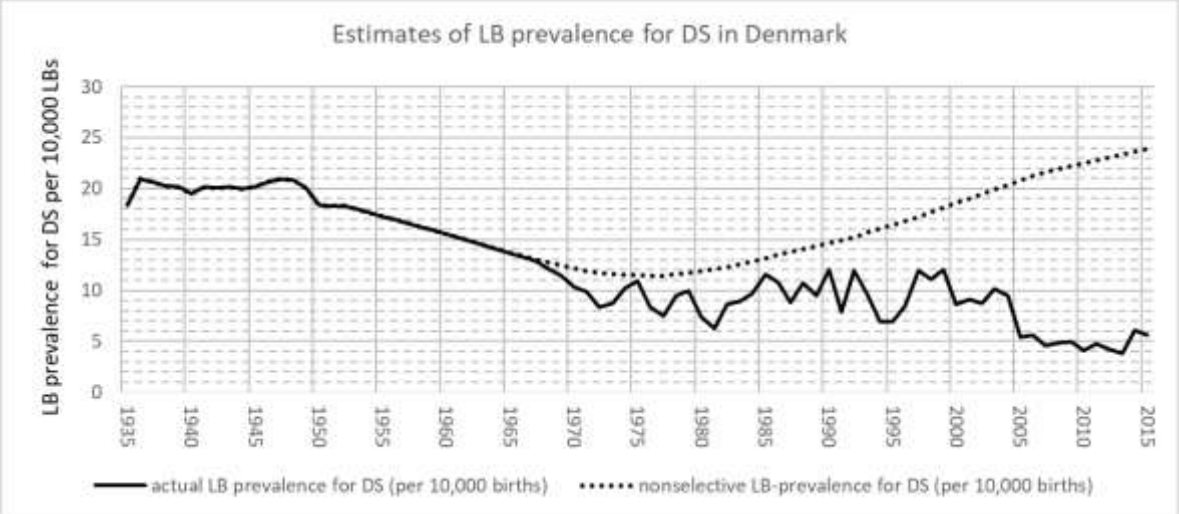

Estimated people with DS in Switzerland, 1950-2015
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
8
7
6
5
4
3
2
1
0
1618
2034
2518
3091
3608
3947
4152
4332
4528
4668
4623
4436
4328
4241
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

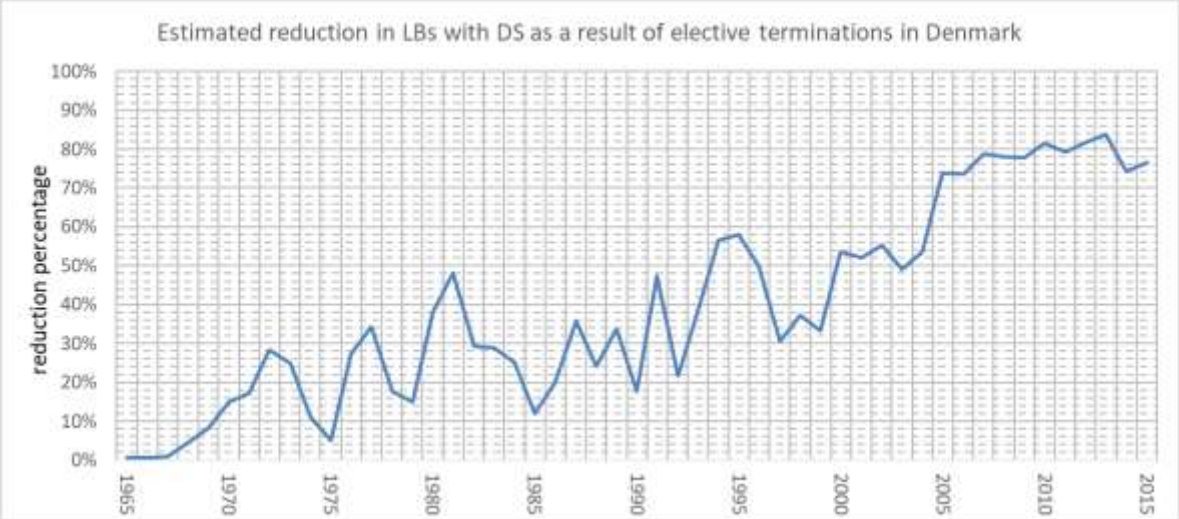

Estimated people with DS in Switzerland by age group, as of 2015
500
450
400
350
300
250
200
150
100
50
0
10
9
8
7
6
5
4
3
2
1
0
375
306
170
243
359
355
298
290
376
468
432
286
159
79
33
9
3
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

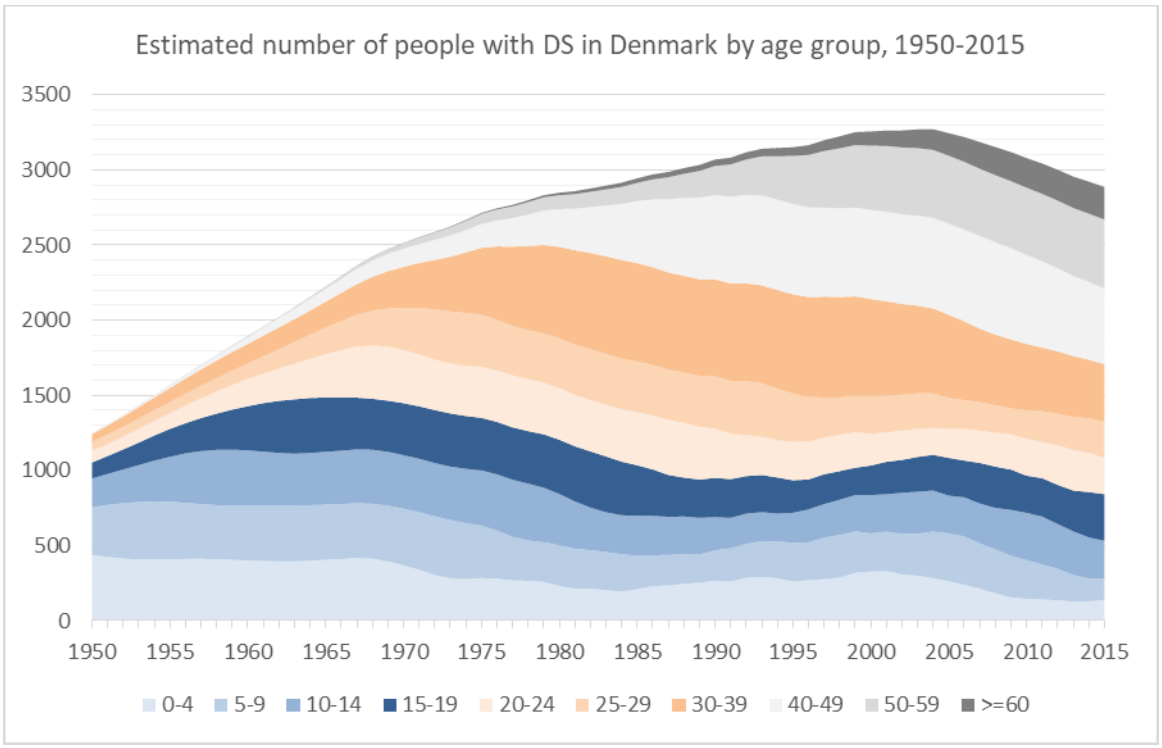
Northern Europe

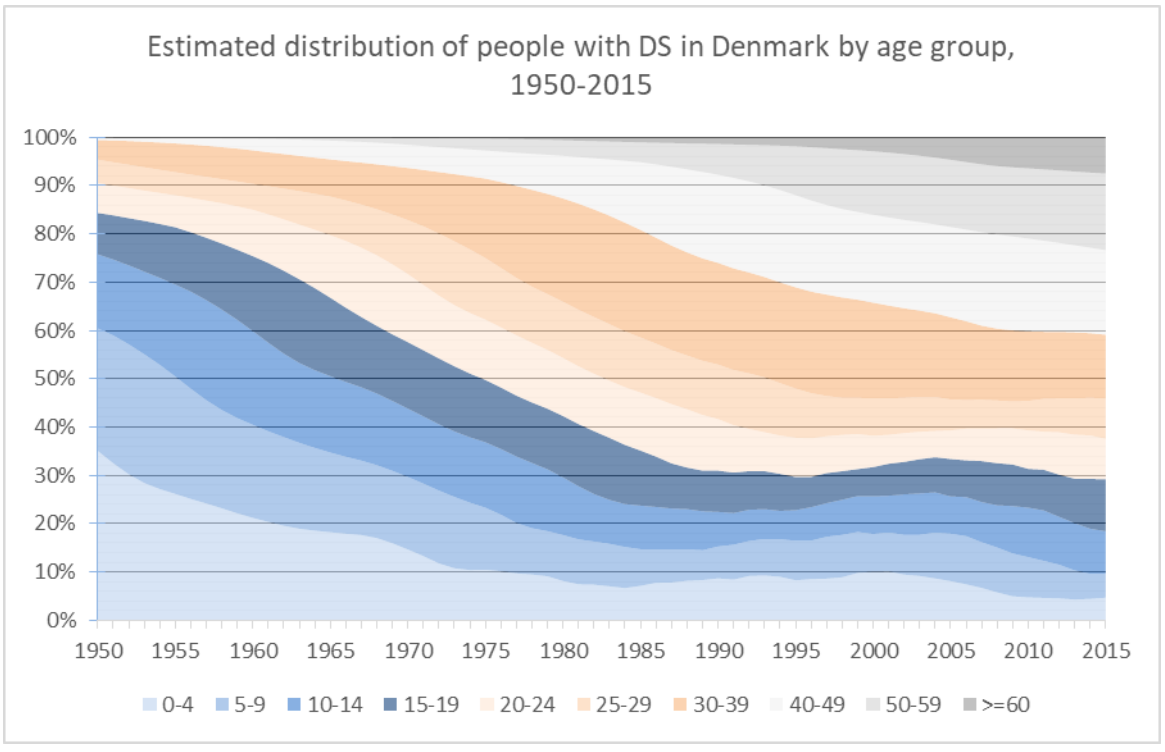
Denmark

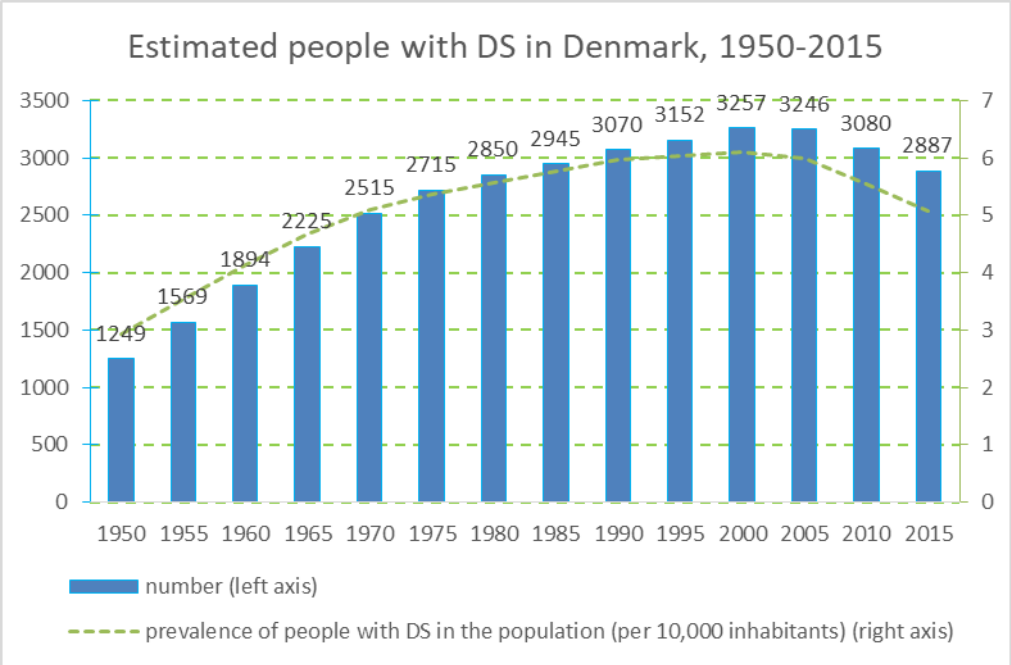


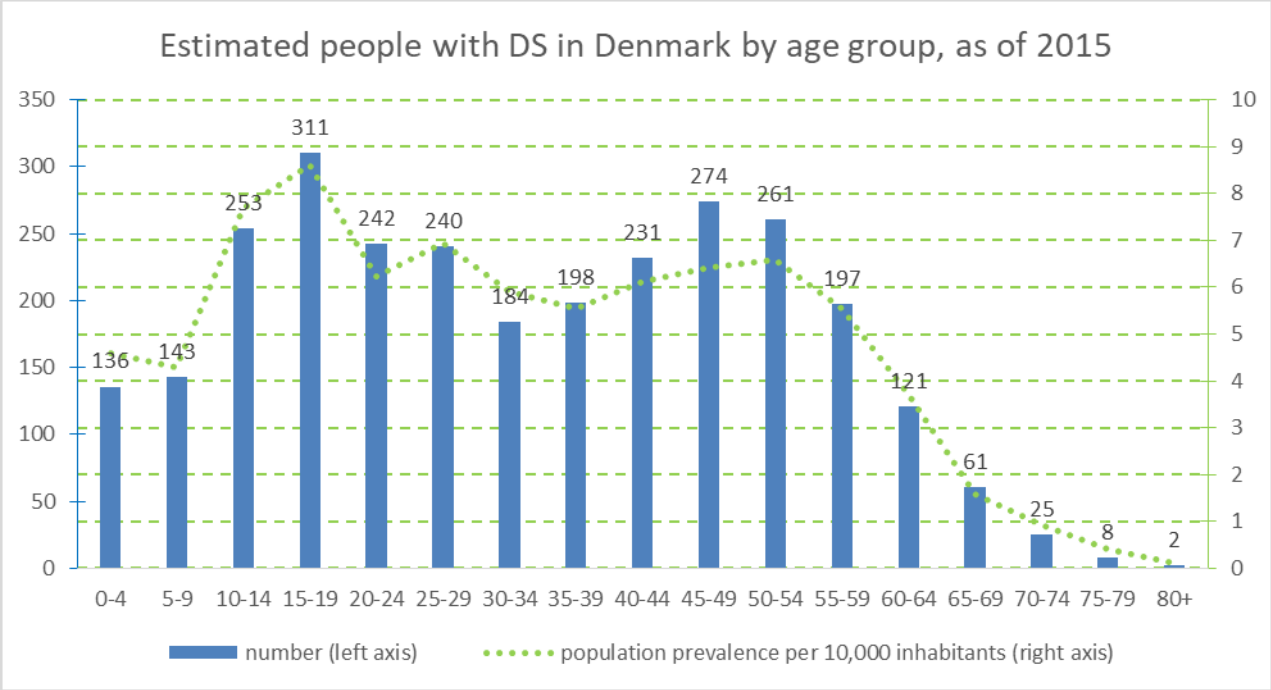




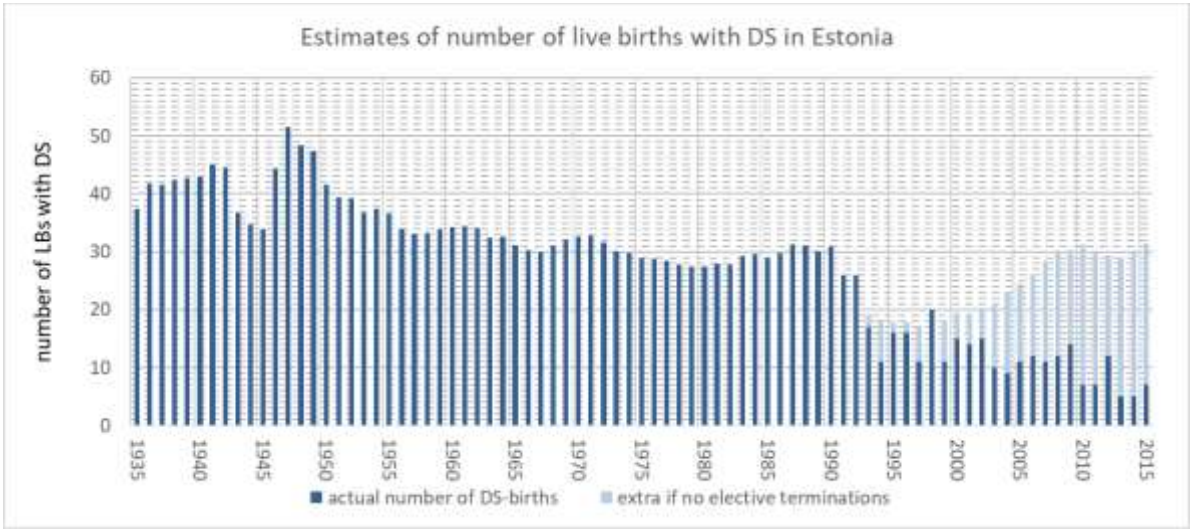

Estimated number of people with DS in Denmark by age group, 1950-2015
3500
3000
2500
2000
1500
1000
500
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

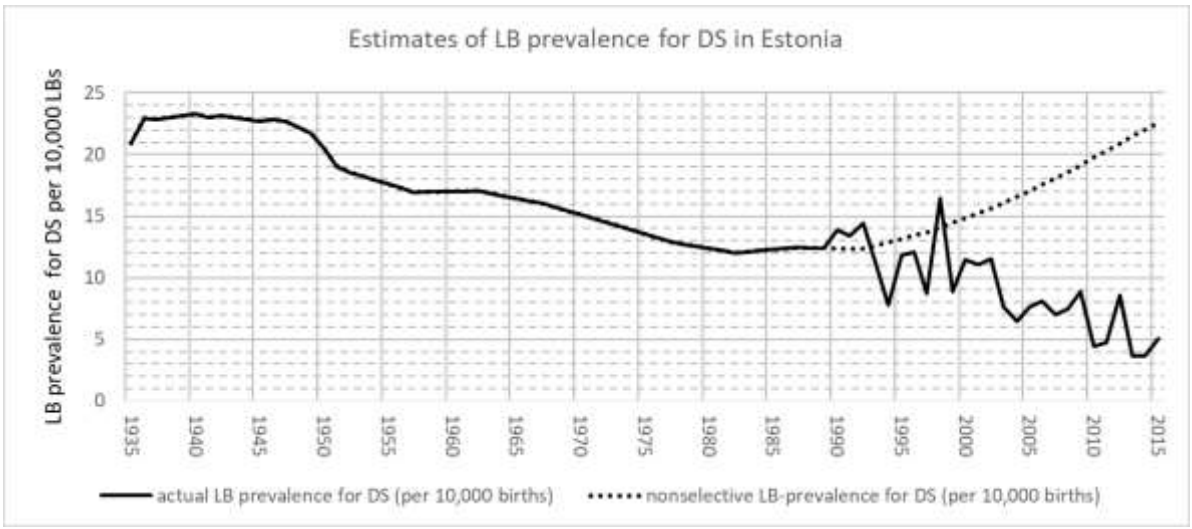

Estimated distribution of people with DS in Denmark by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

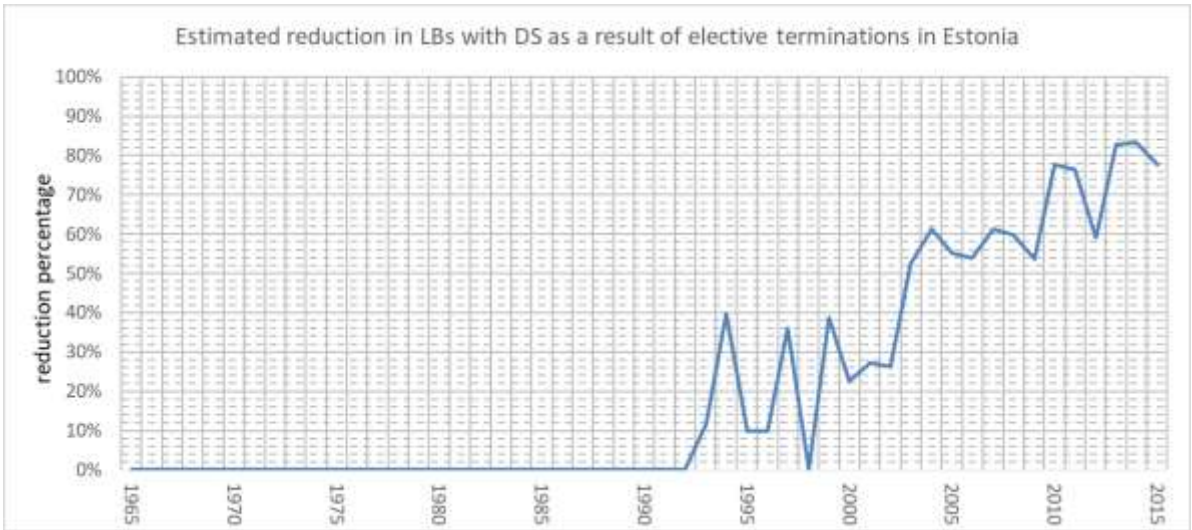

Estimated people with DS in Denmark, 1950-2015
3500
3000
2500
2000
1500
1000
500
0
7
6
5
4
3
2
1
0
1249
1569
1894
2225
2515
2715
2850
2945
3070
3152
3257
3246
3080
2887
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Denmark by age group, as of 2015
350
300
250
200
150
100
50
0
10
9
8
7
6
5
4
3
2
1
0
136
143
253
311
242
240
184
198
231
274
261
197
121
61
25
8
2
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Estonia

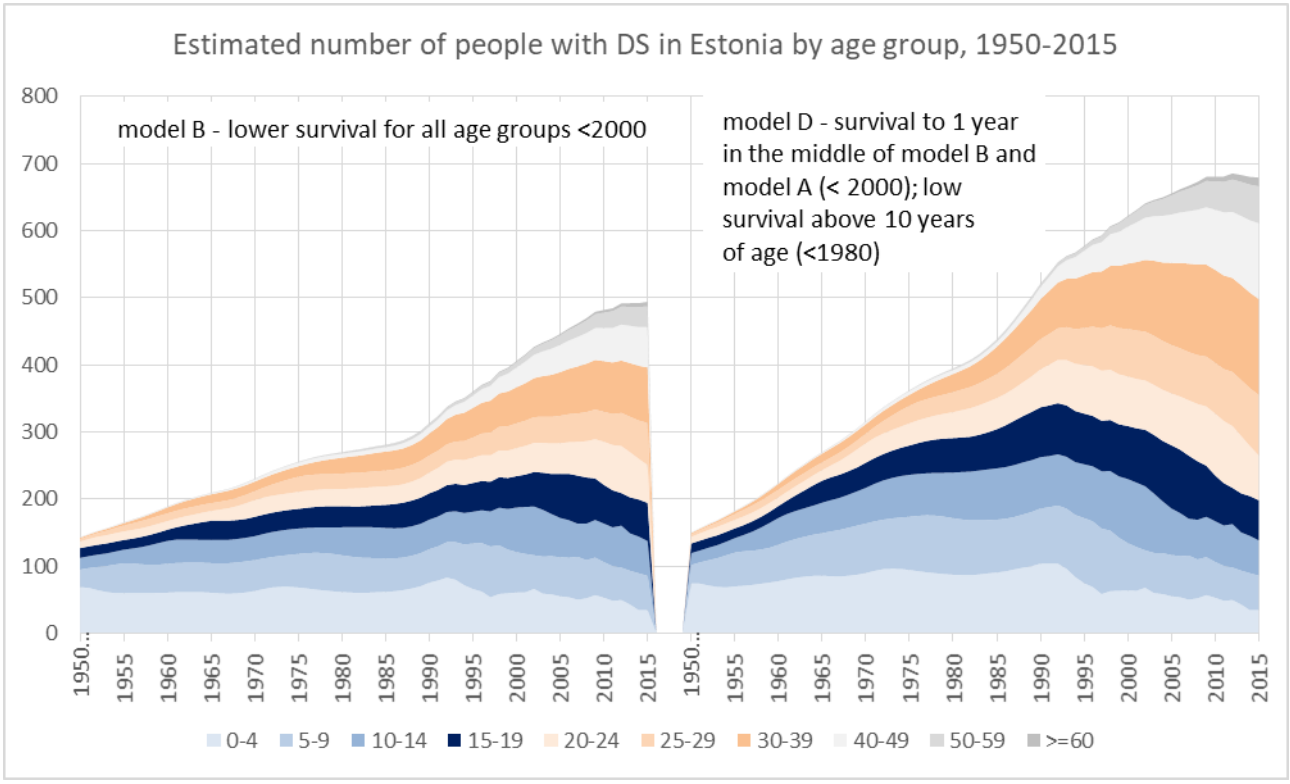


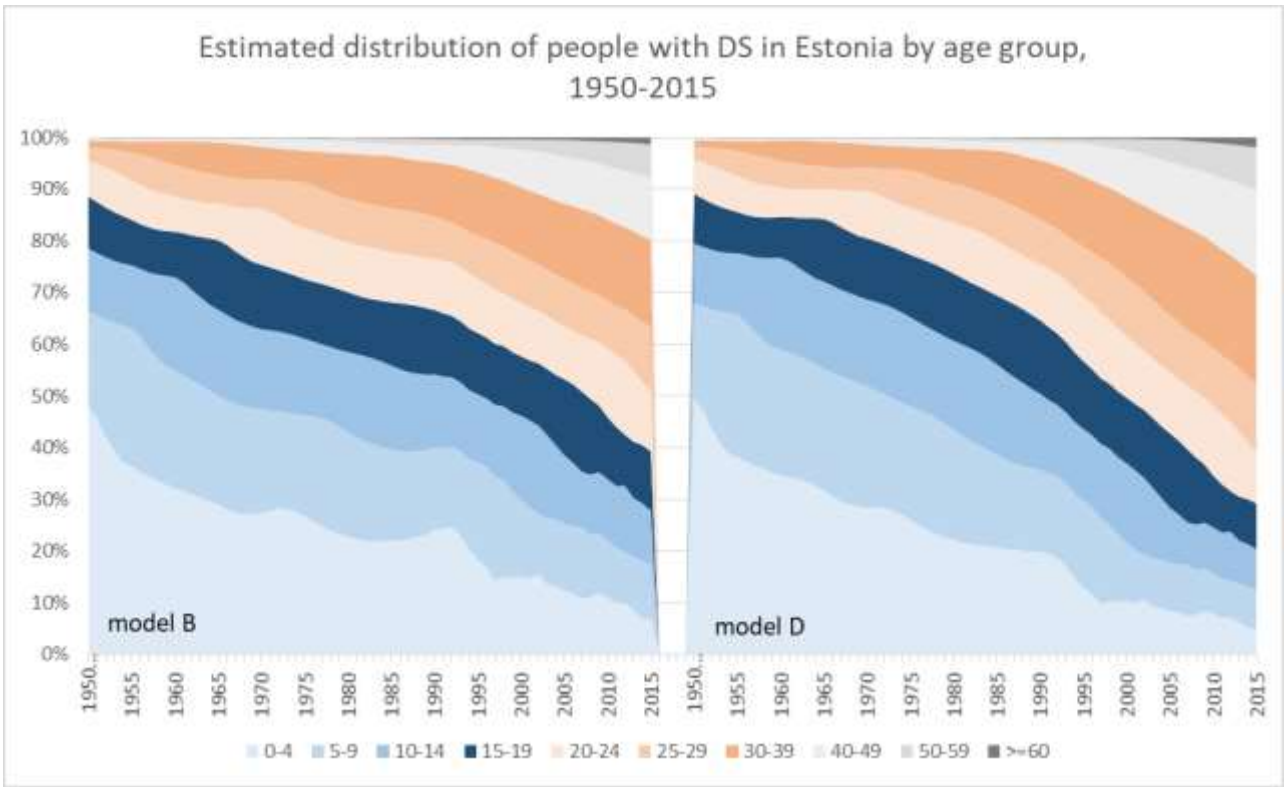


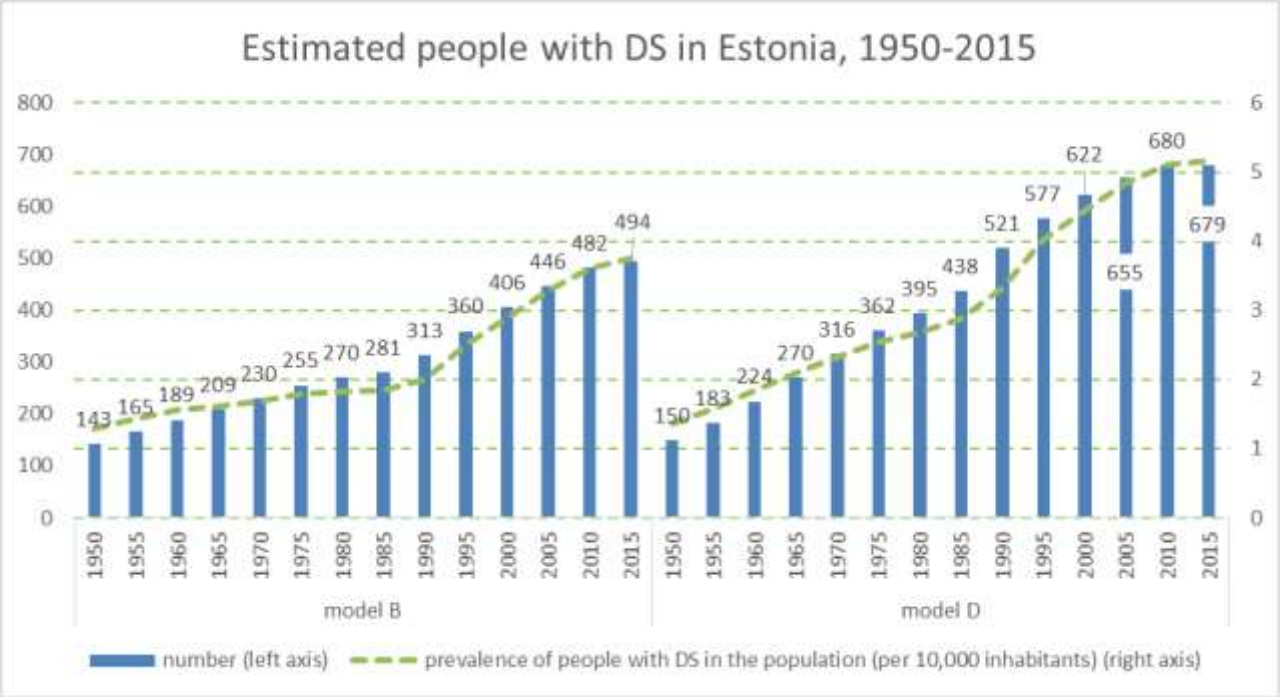


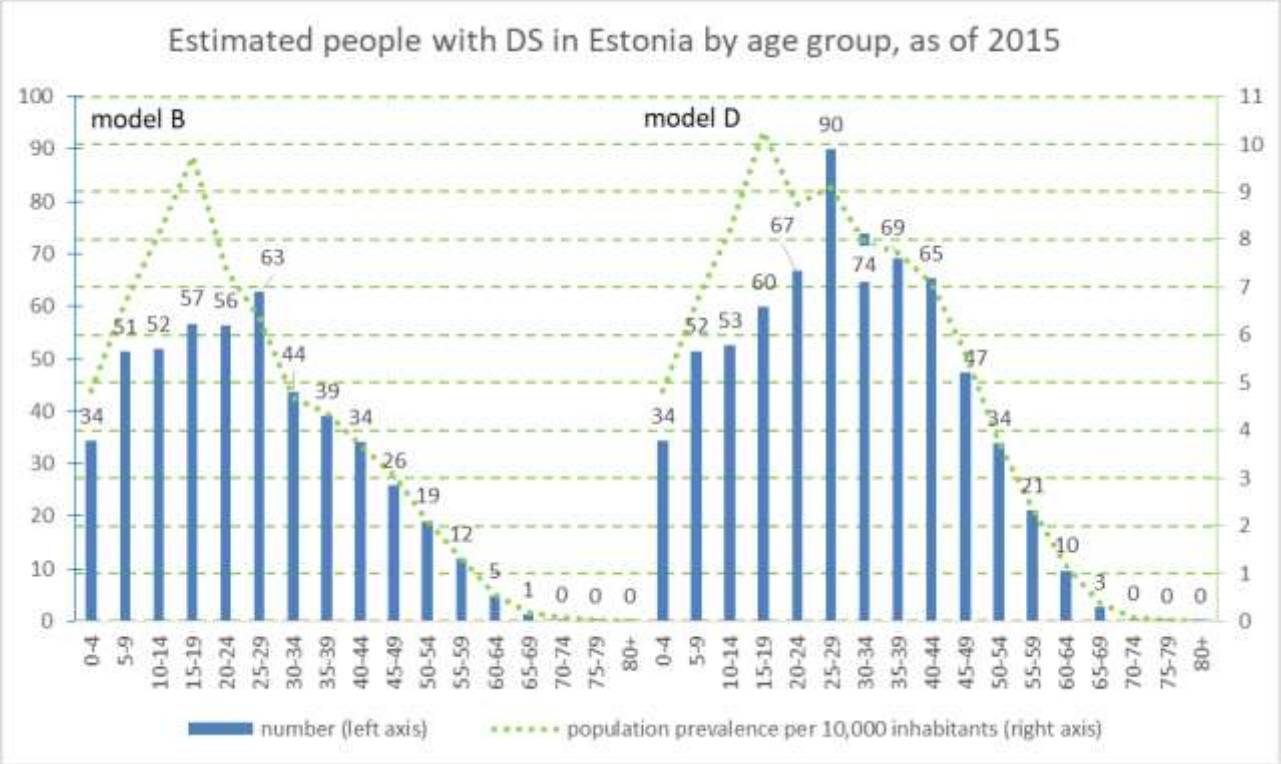
In the graph, negative reduction percentages (if nonselective prevalence is smaller than actual prevalence) have been set at zero after 1989. This is the case for 1998 (with a reduction of -17%). This can be a result of some random fluctuation in a relatively small population.

Model A projects 926 people with DS alive in 2015, which corresponds to a population prevalence of 7.0 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths of people with DS (see S5C). Model C projects 843 people with DS (6.4 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Estonia, Model D seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics (see S5C).

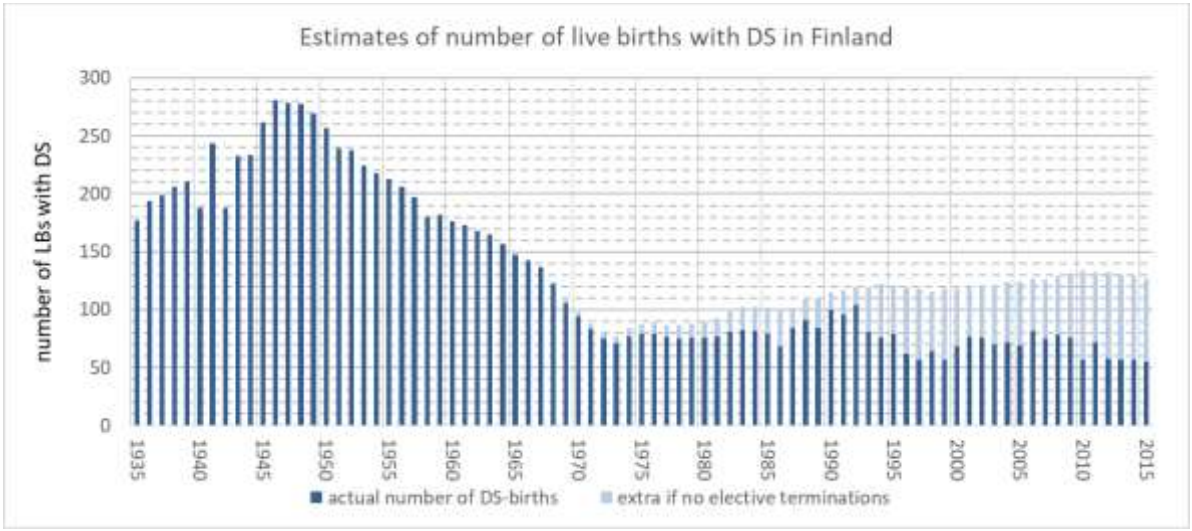


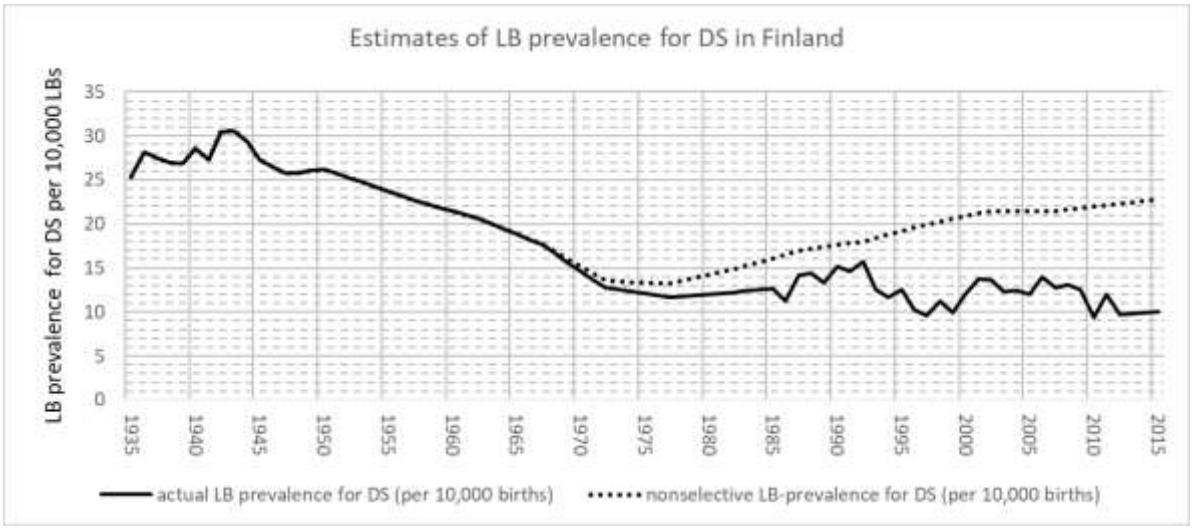


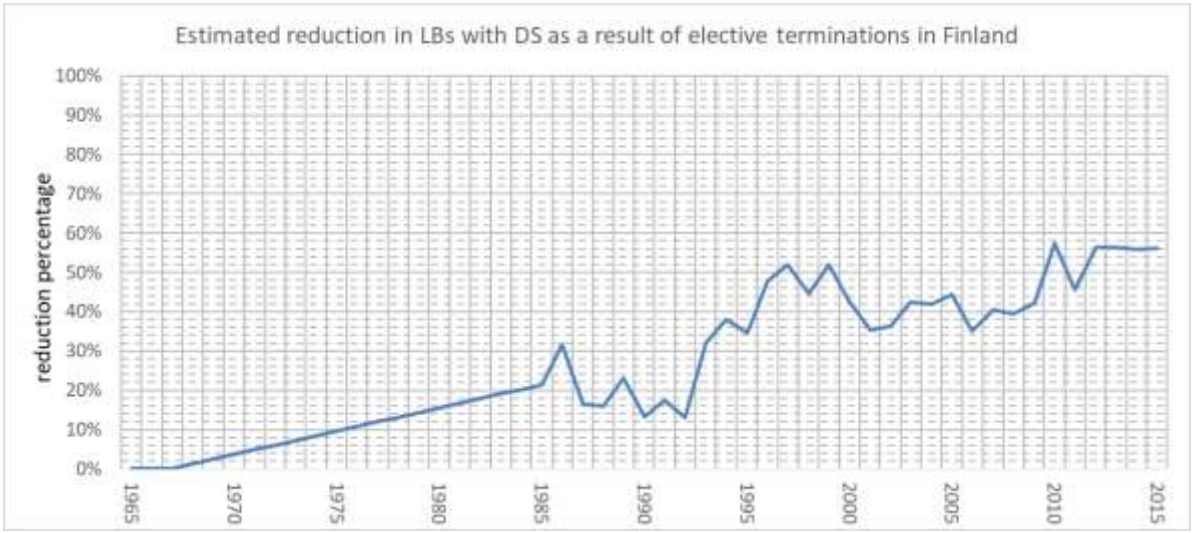

Estimated people with DS in Estonia, 1950-2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

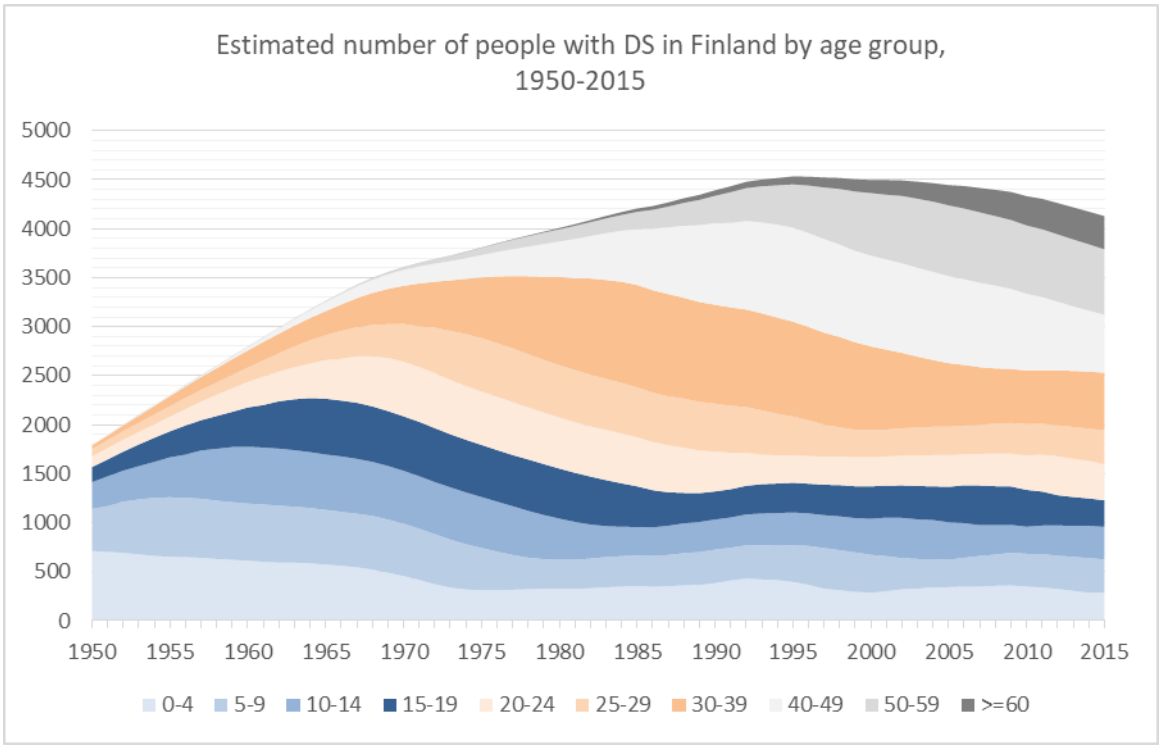

Estimated people with DS in Estonia by age group, as of 2015
model B
model D
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

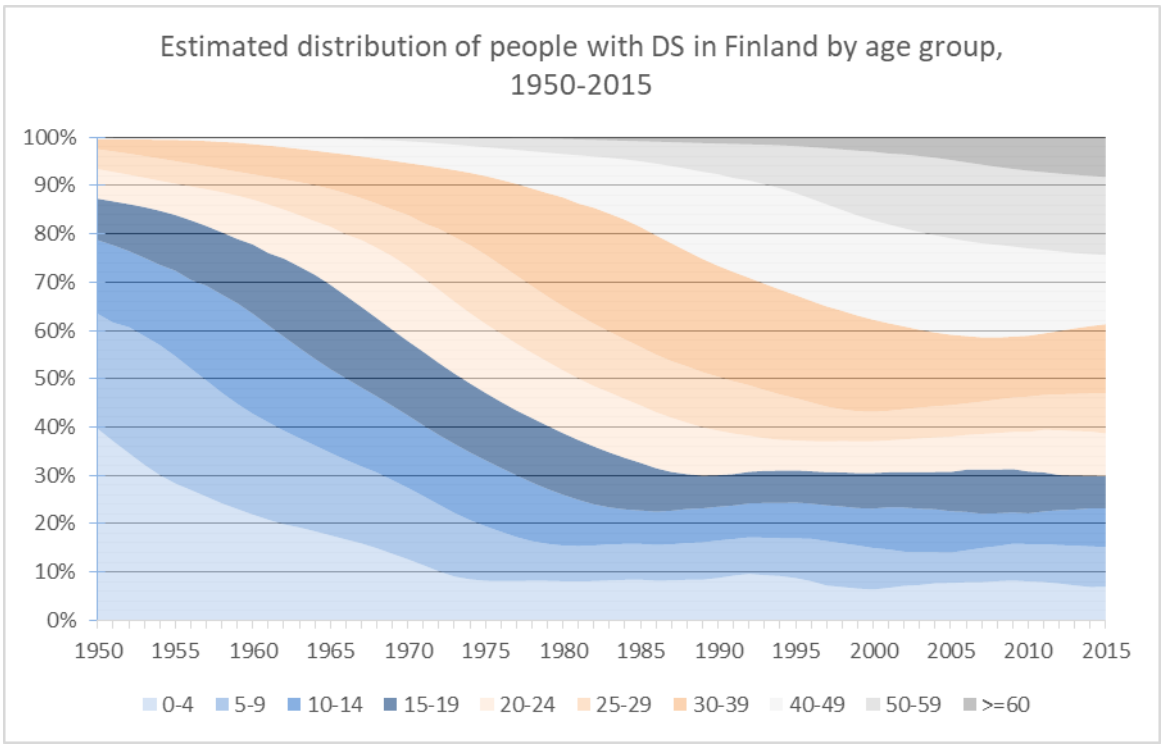
Finland

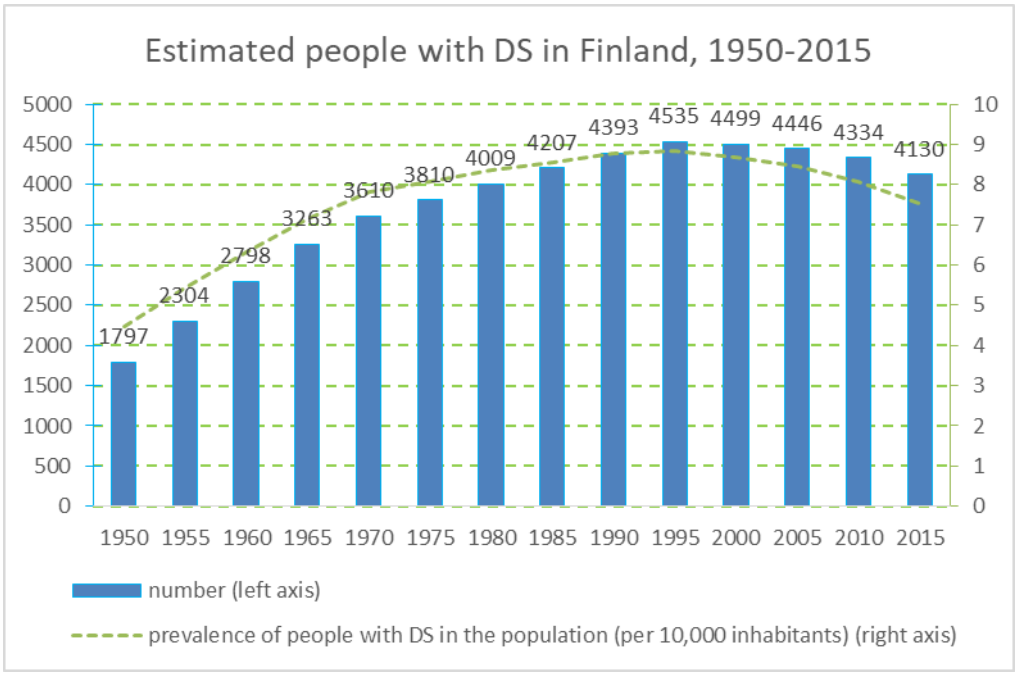

Estimates of number of live births with DS in Finland
number of LBs with DS
300
250
200
150
100
50
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

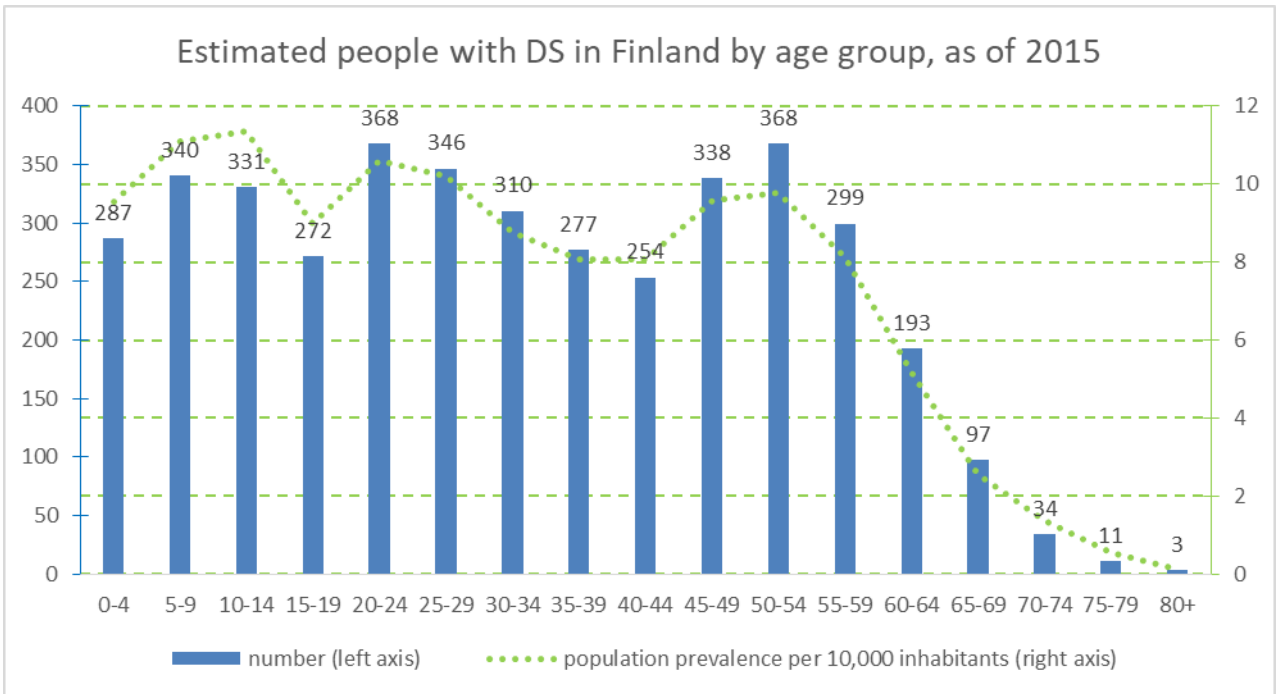

Estimates of LB prevalence for DS in Finland
LB prevalence for DS per 10,000 LBs
35
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Finland
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015


Estimated number of people with DS in Finland by age group, 1950-2015
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

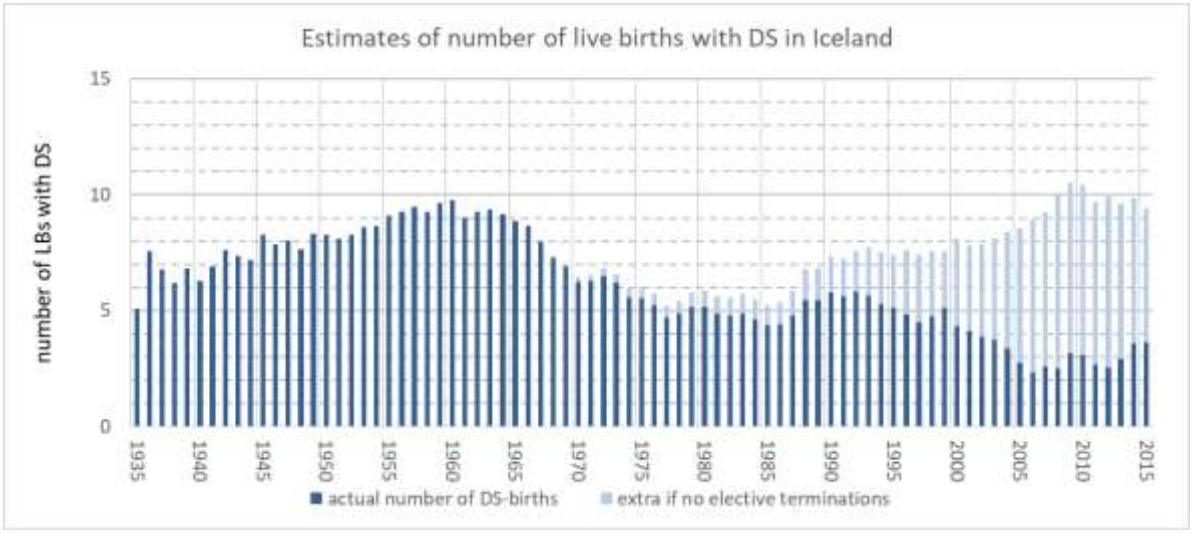

Estimated distribution of people with DS in Finland by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

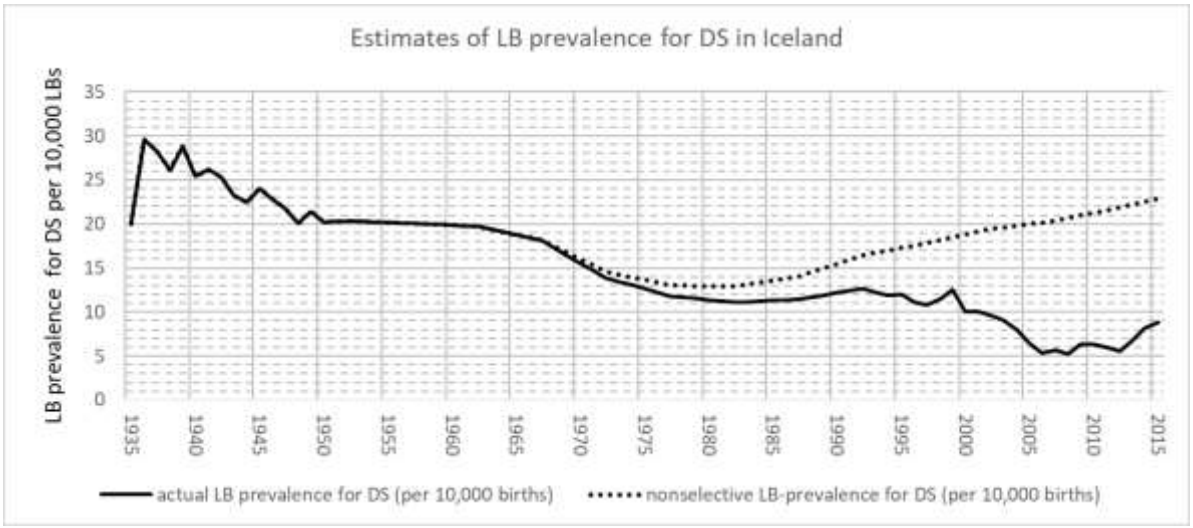

Estimated people with DS in Finland, 1950-2015
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10
9
8
7
6
5
4
3
2
1
0
1797
2304
2798
3263
3610
3810
4009
4207
4393
4535
4499
4446
4334
4130
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

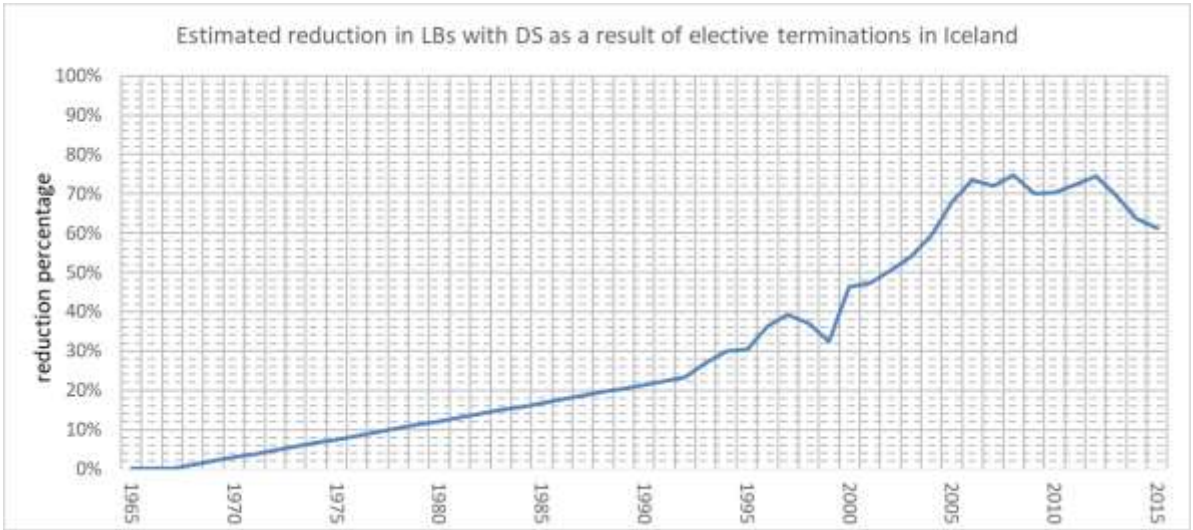

Estimated people with DS in Finland by age group, as of 2015
400
350
300
250
200
150
100
50
0
12
10
8
6
4
2
0
287
340
331
272
368
346
310
277
254
338
368
299
193
97
34
11
3
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

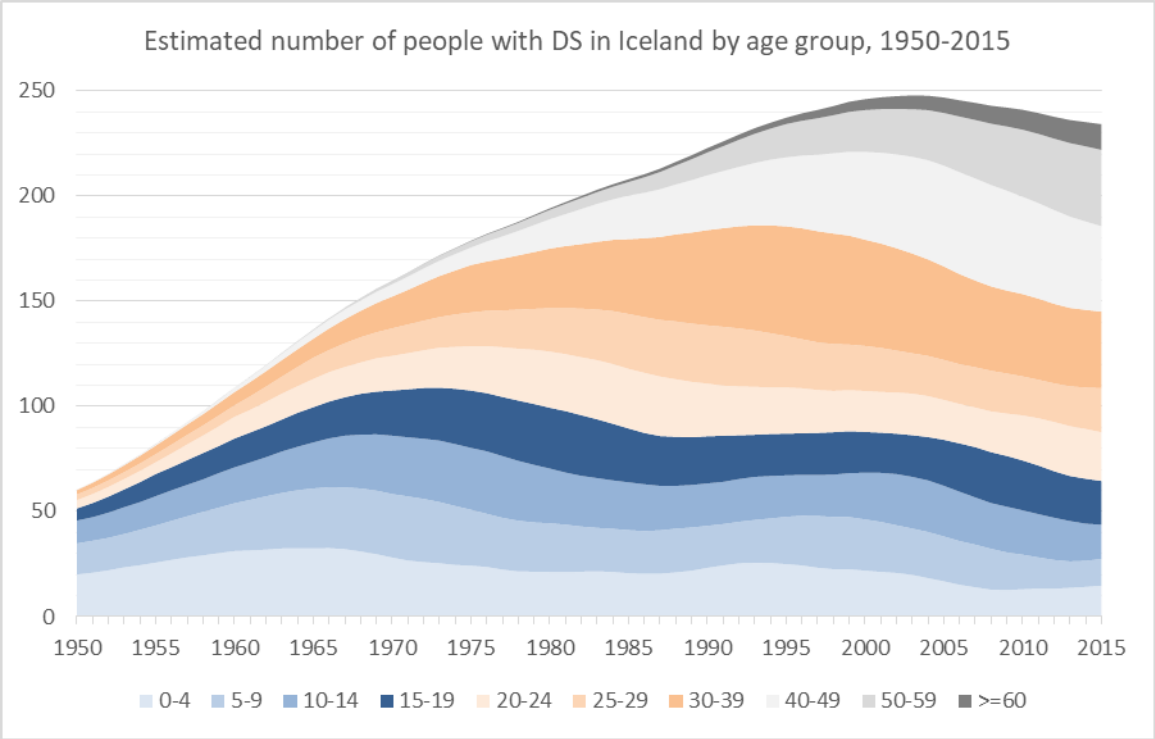
Iceland

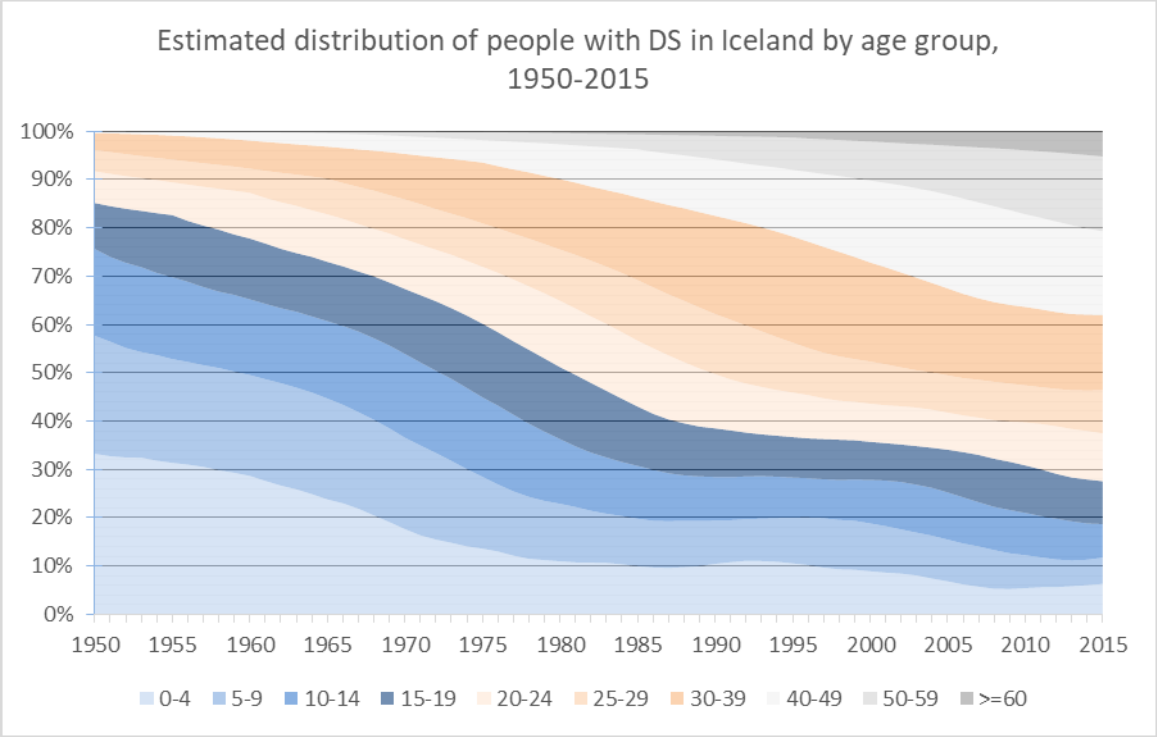
(For 1990 onwards, estimates of actual prevalence are based on 5-year running averages of reduction percentage (based on counts) projected onto the estimates of nonselective prevalence.)

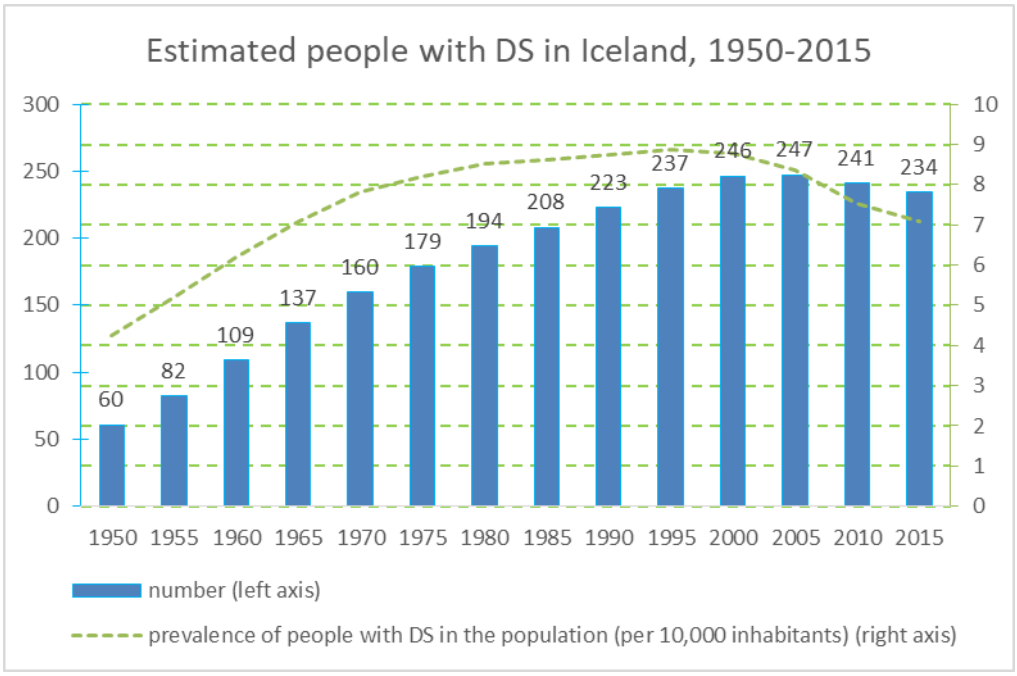


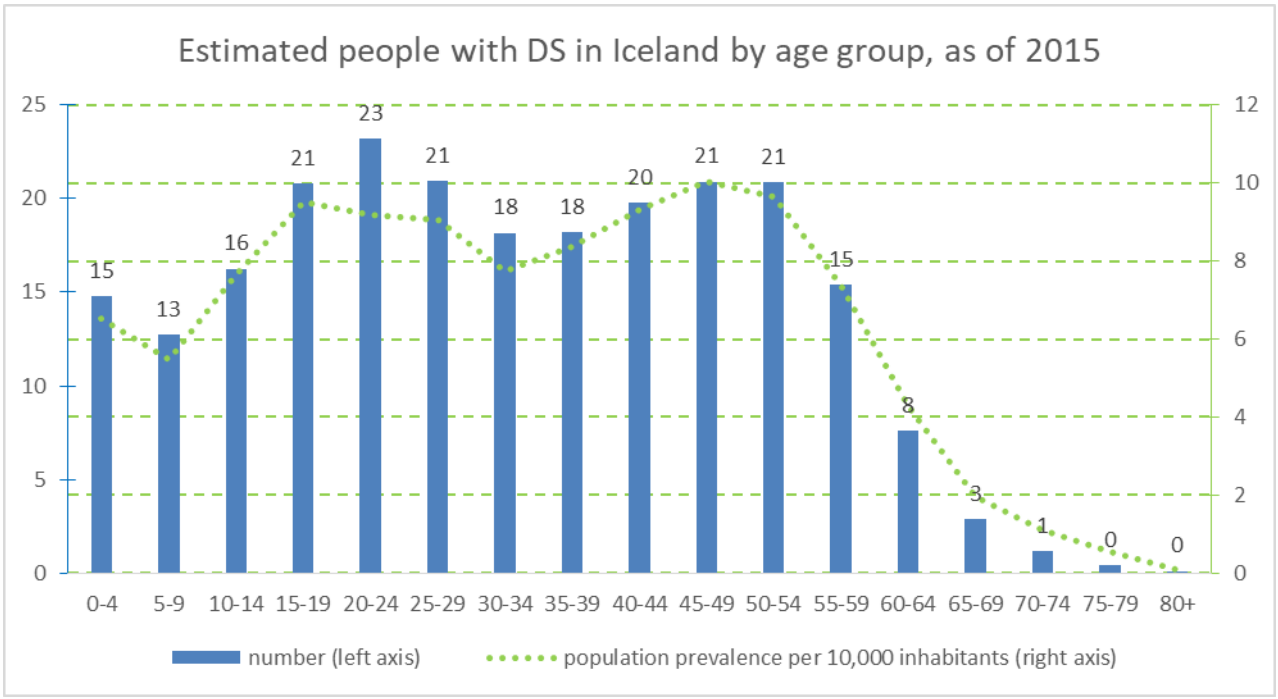




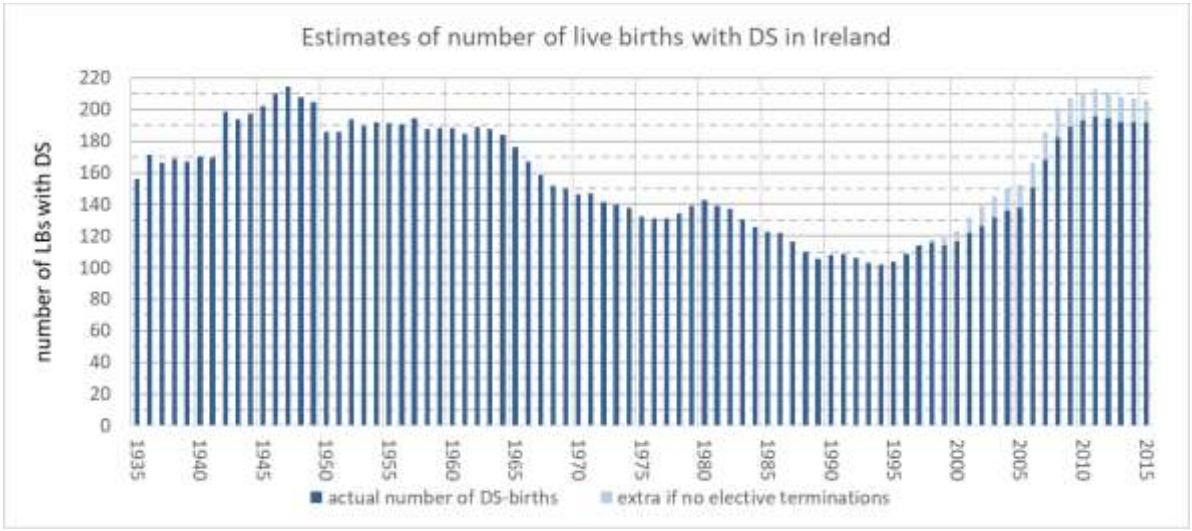

Estimated number of people with DS in Iceland by age group, 1950-2015
250
200
150
100
50
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

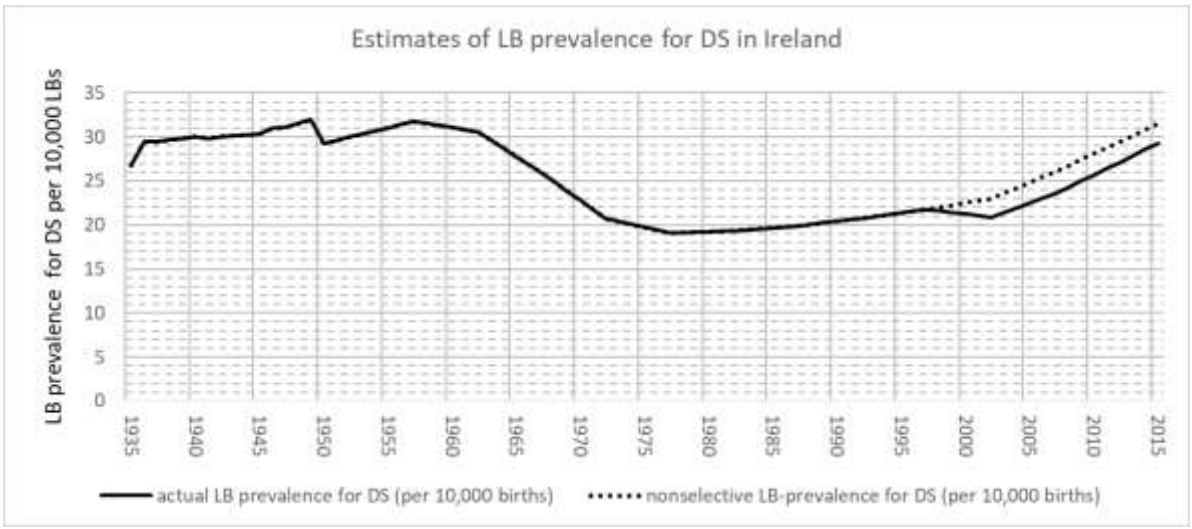

Estimated distribution of people with DS in Iceland by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

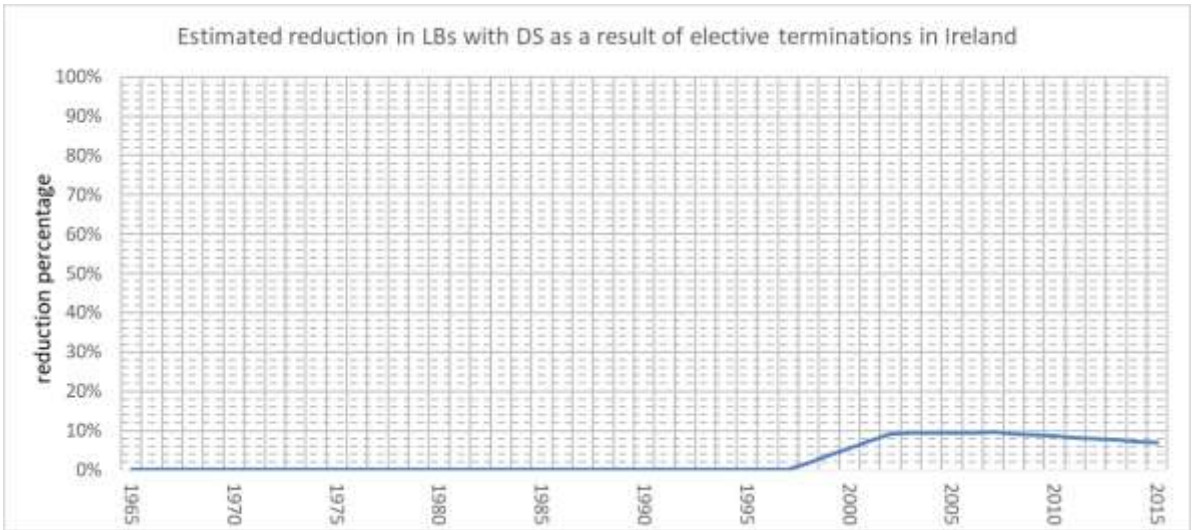

Estimated people with DS in Iceland, 1950-2015
300
250
200
150
100
50
0
10
9
8
7
6
5
4
3
2
1
0
60
82
109
137
160
179
194
208
223
237
246
247
241
234
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

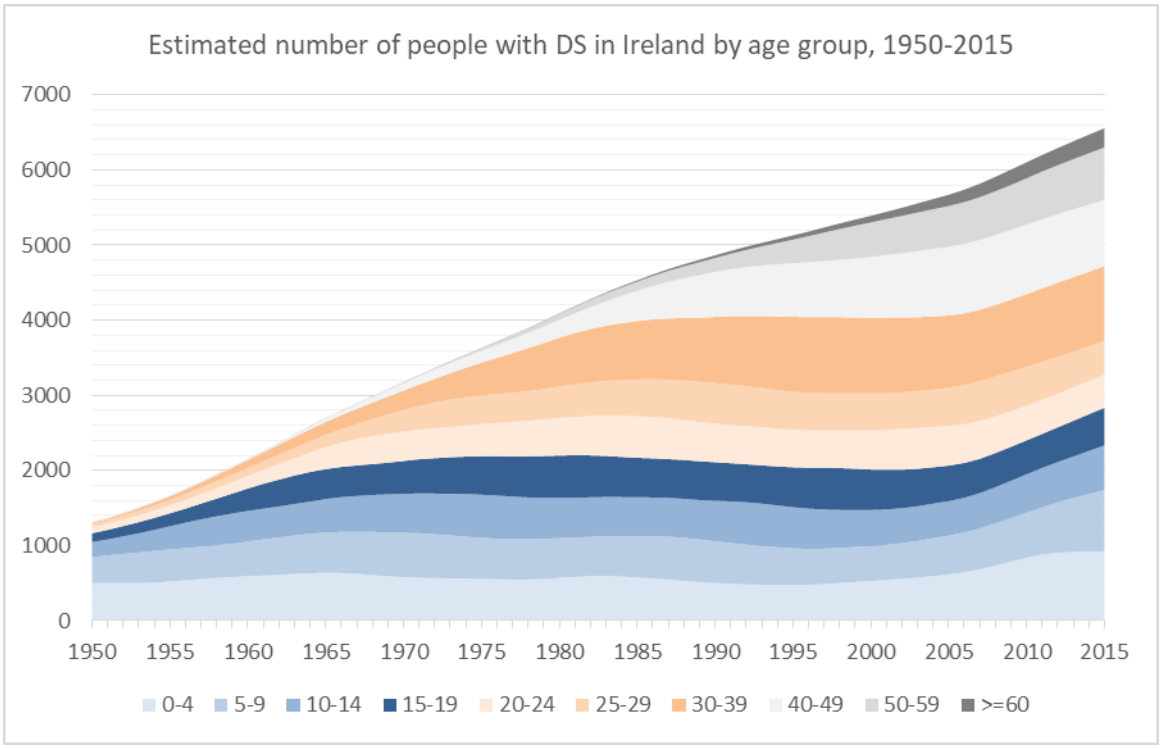

Estimated people with DS in Iceland by age group, as of 2015
25
20
15
10
5
0
12
10
8
6
4
2
0
15
13
16
21
23
21
18
18
20
21
21
15
8
3
1
0
0
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

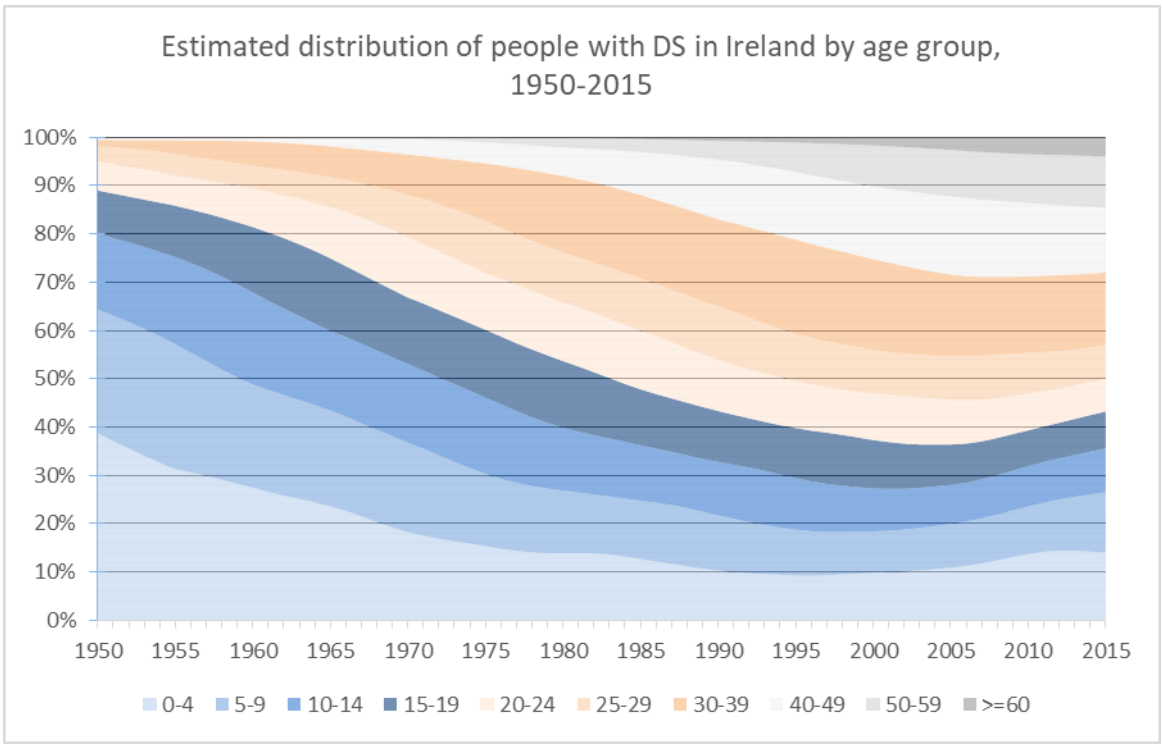
Ireland

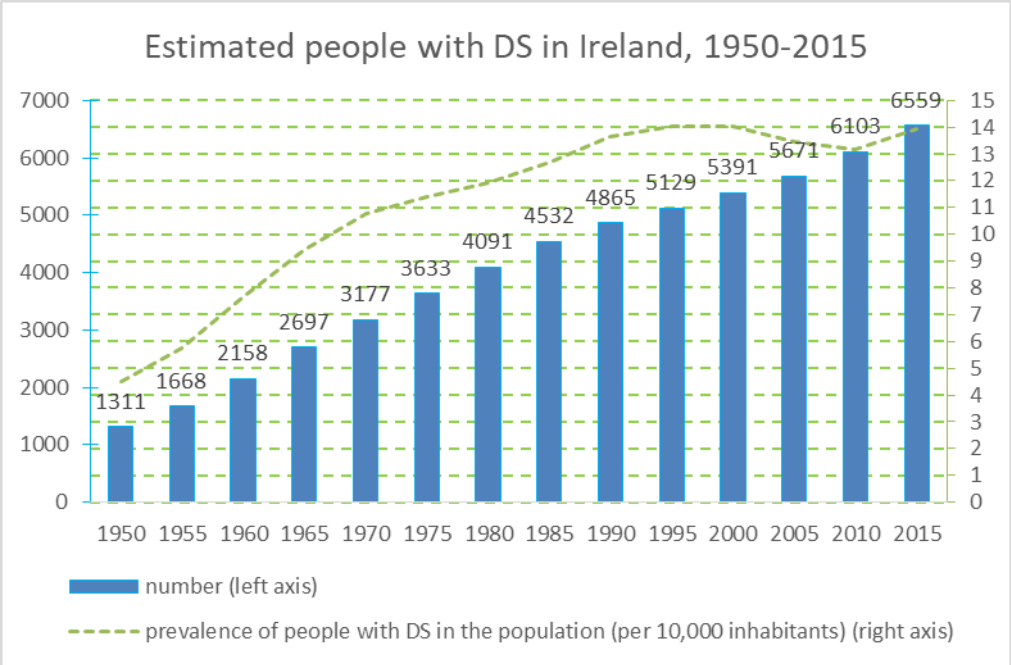

Estimates of number of live births with DS in Ireland
number of LBs with DS
220
200
180
160
140
120
100
80
60
40
20
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

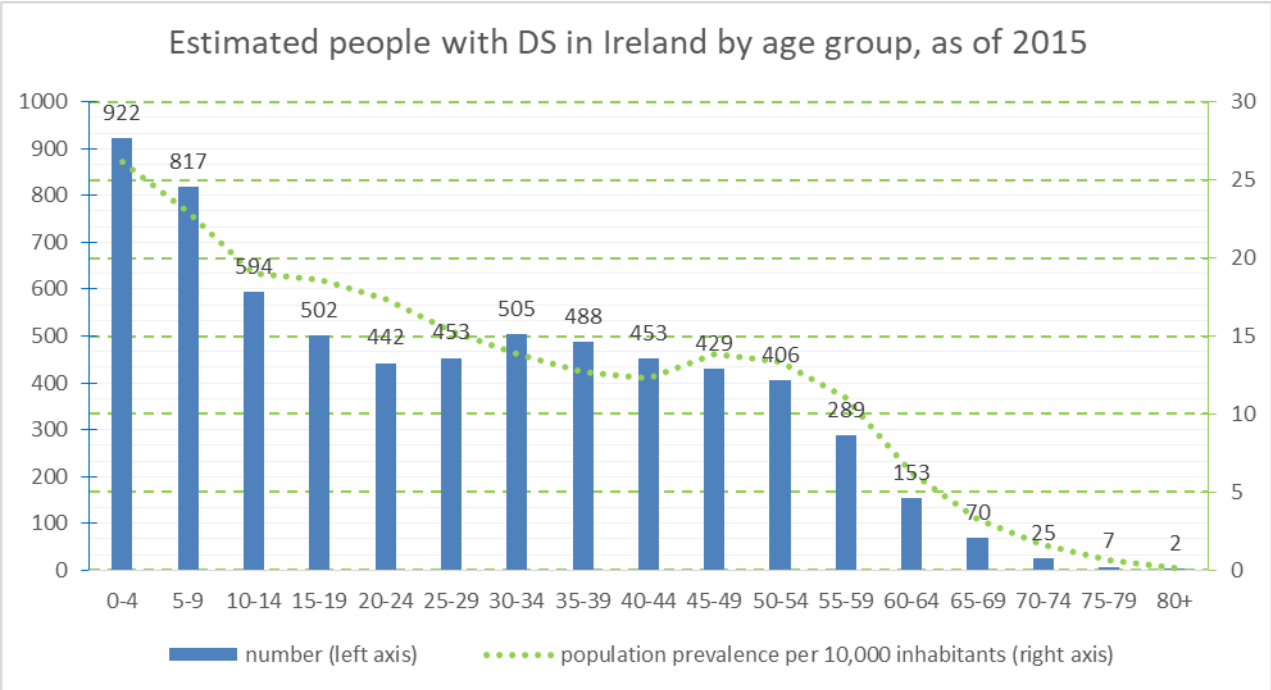

Estimates of LB prevalence for DS in Ireland
LB prevalence for DS per 10,000 LBs
35
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Ireland
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

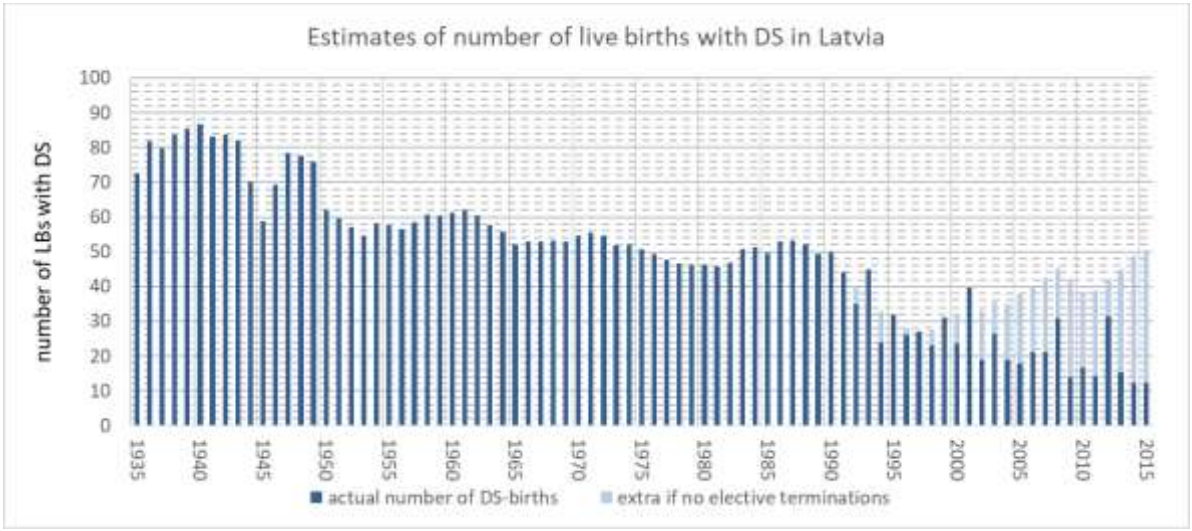

Estimated number of people with DS in Ireland by age group, 1950-2015
7000
6000
5000
4000
3000
2000
1000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

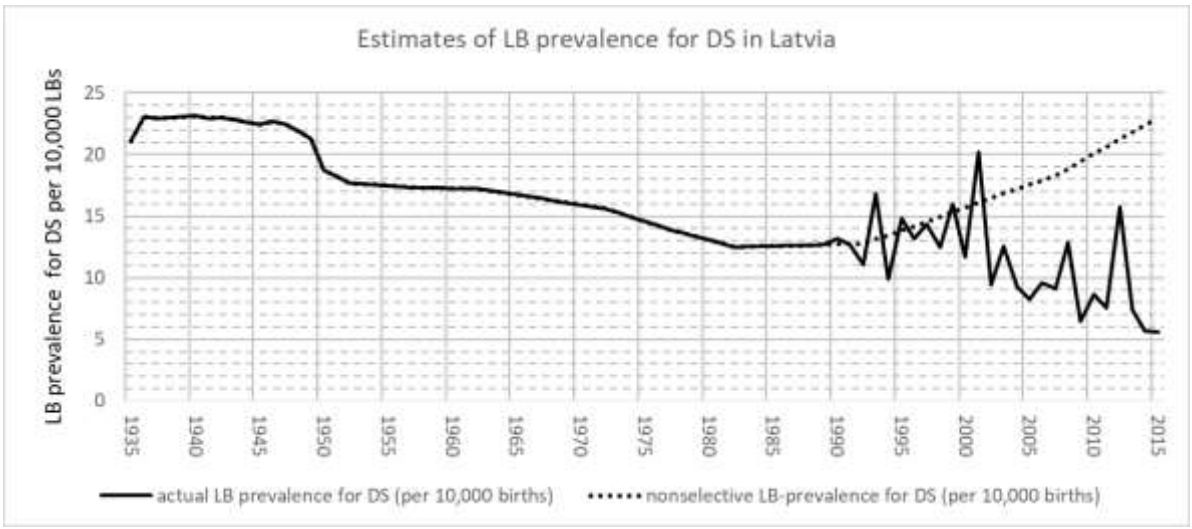

Estimated distribution of people with DS in Ireland by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

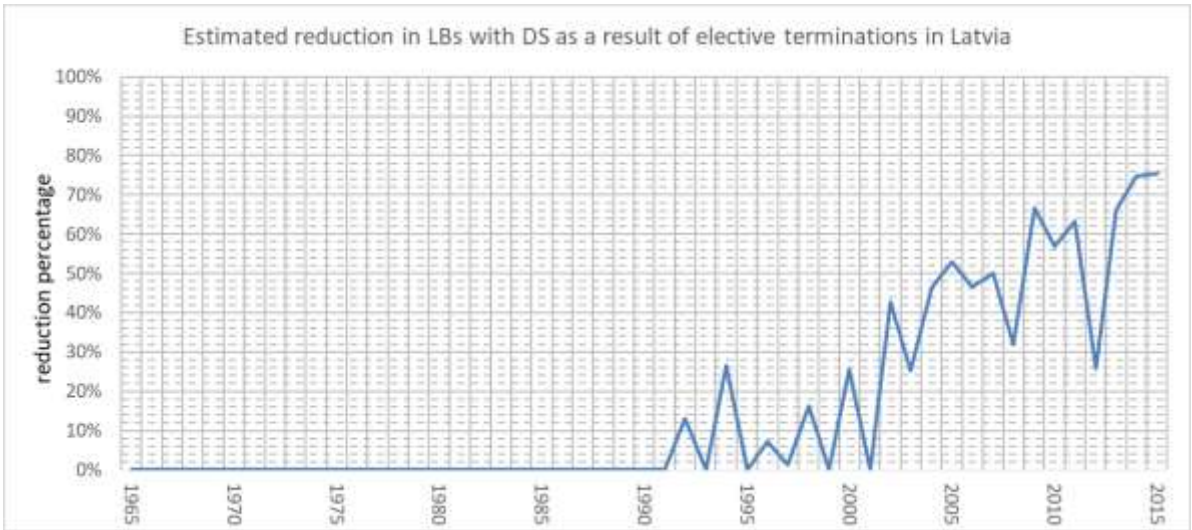

Estimated people with DS in Ireland, 1950-2015
7000
6000
5000
4000
3000
2000
1000
0
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1311
1668
2158
2697
3177
3633
4091
4532
4865
5129
5391
5671
6103
6559
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Ireland by age group, as of 2015
1000
900
800
700
600
500
400
300
200
100
0
30
25
20
15
10
5
0
922
817
594
502
442
453
505
488
453
429
406
289
153
70
25
7
2
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Latvia

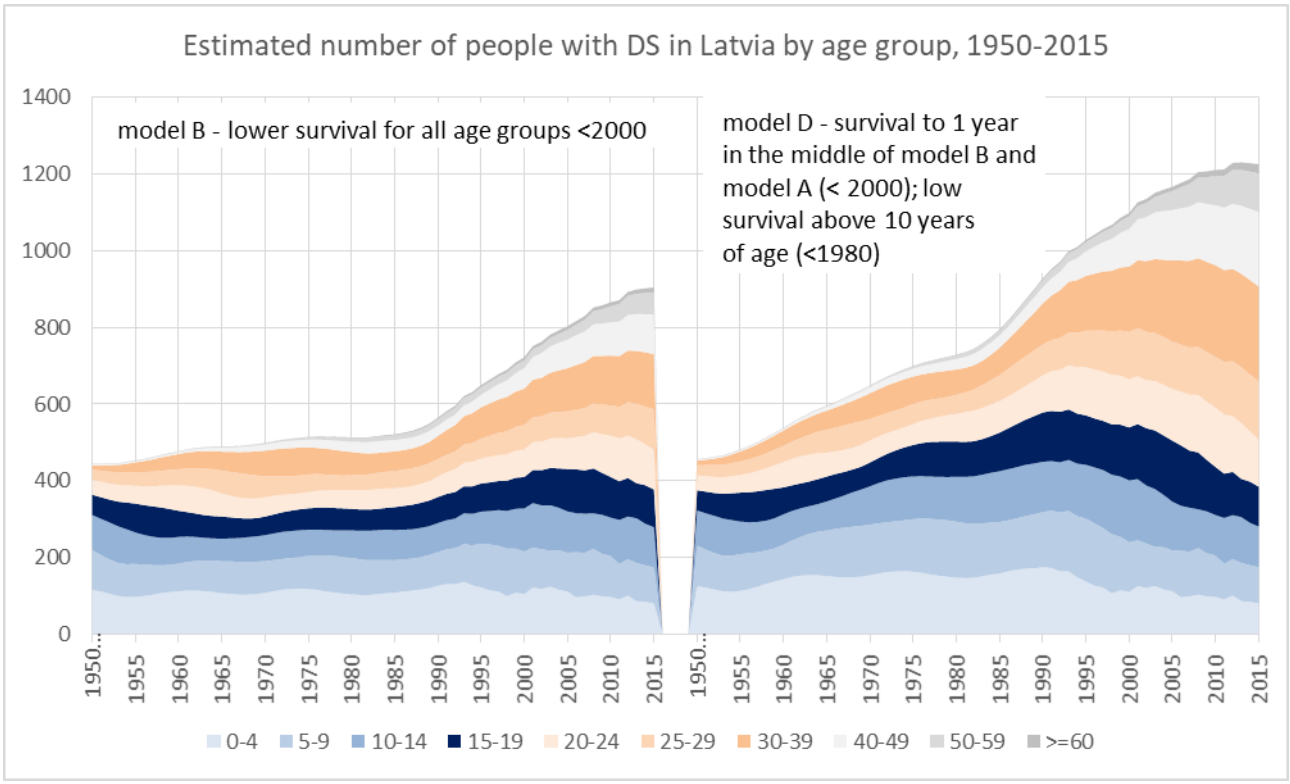


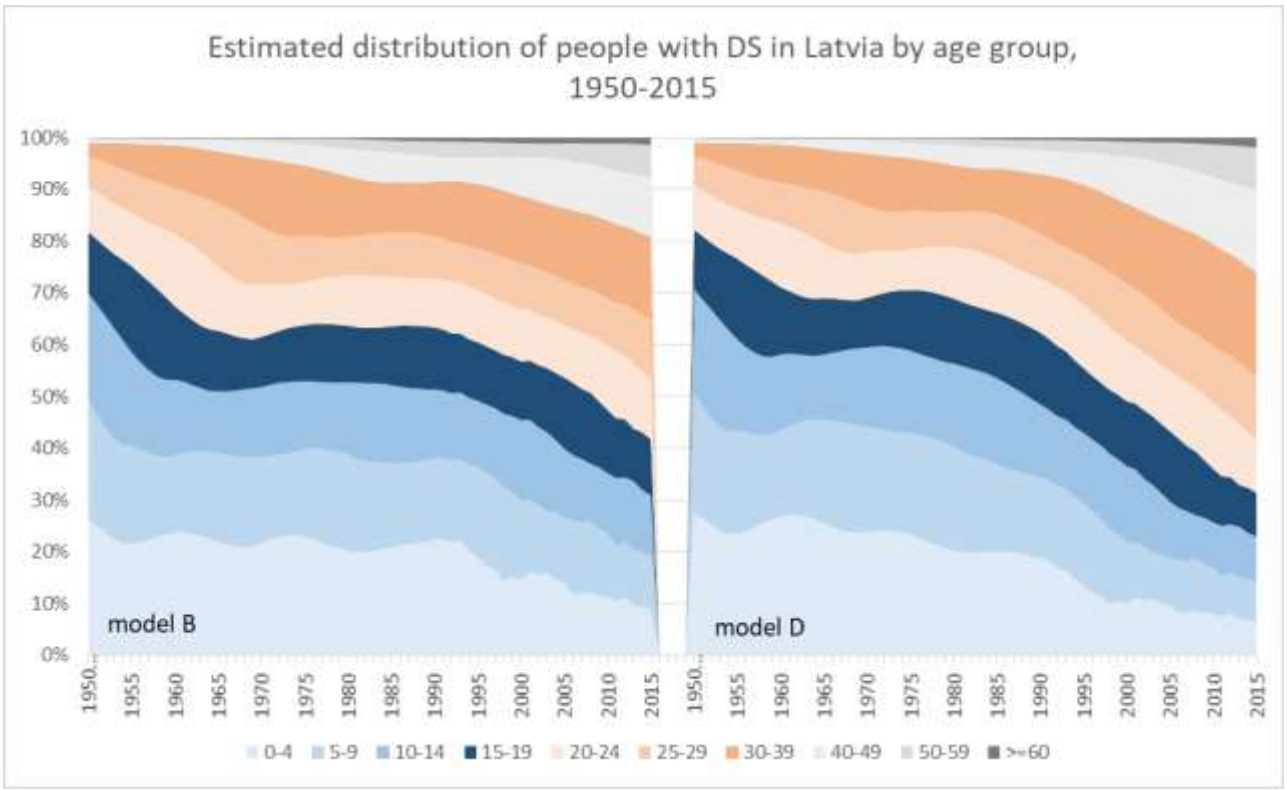


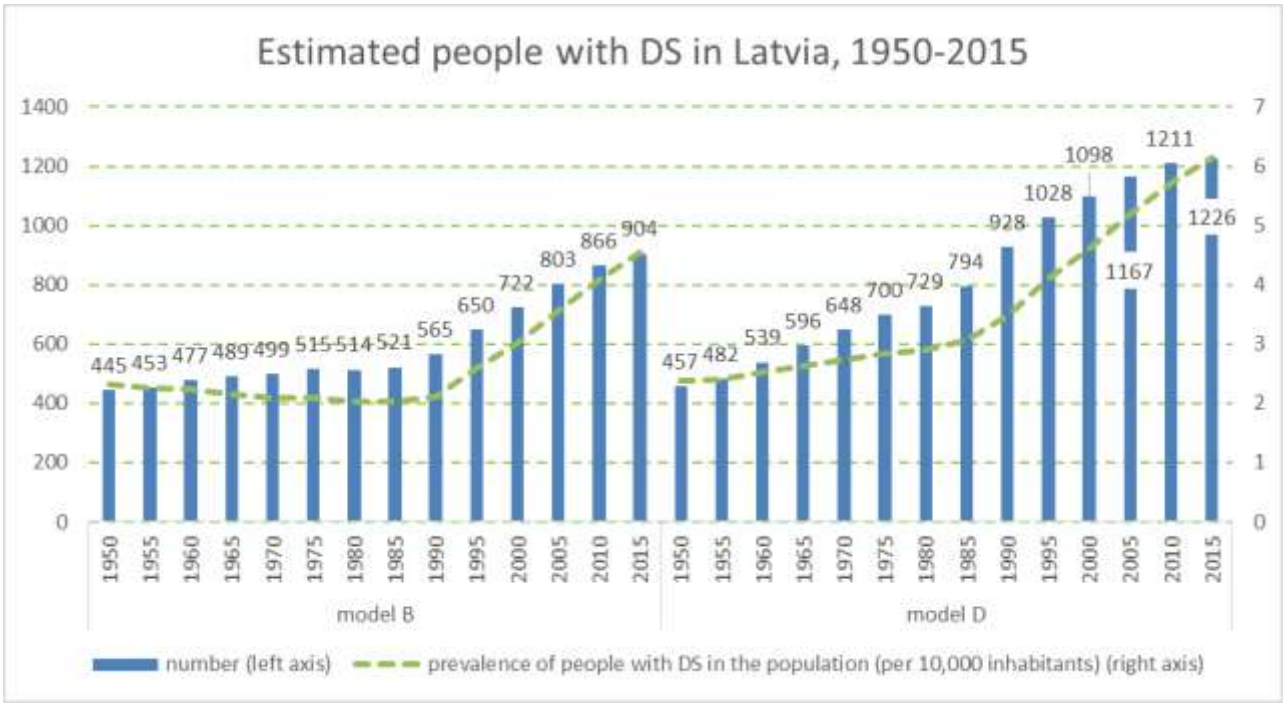


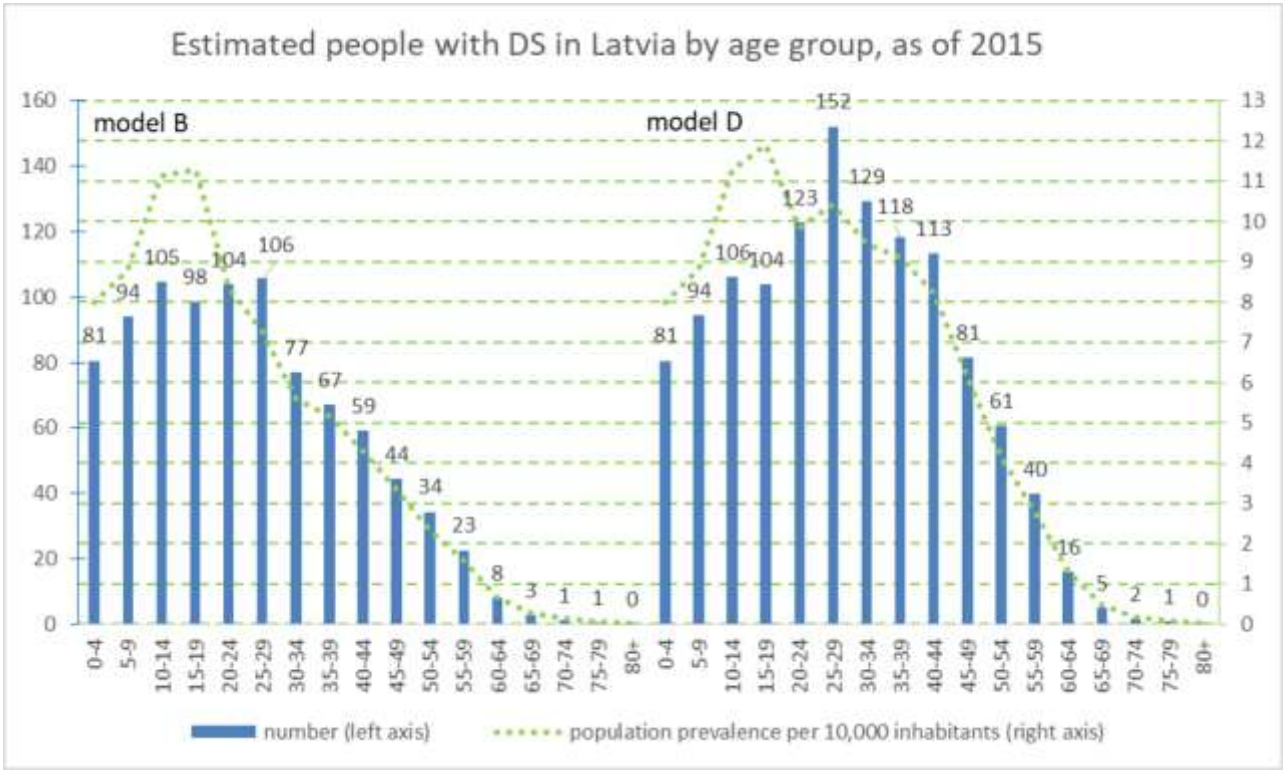
In the graph, negative reduction percentages (if nonselective prevalence is smaller than actual prevalence) have been set at zero after 1989. This is the case for 1990 (with a reduction of -4%), 1993 (-28%), 1995 (-7%), 1999 (-4%), and 2001 (-26%). This can be a result of some random fluctuation in a relatively small population.

Model A projects 1,664 people with DS alive in 2015, which corresponds to a population prevalence of 8.4 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 1,509 people with DS (7.6 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Latvia, it is unclear if Model B or Model D has a better fit with the age distribution of deaths with DS as reported in the national statistics (see S5C).

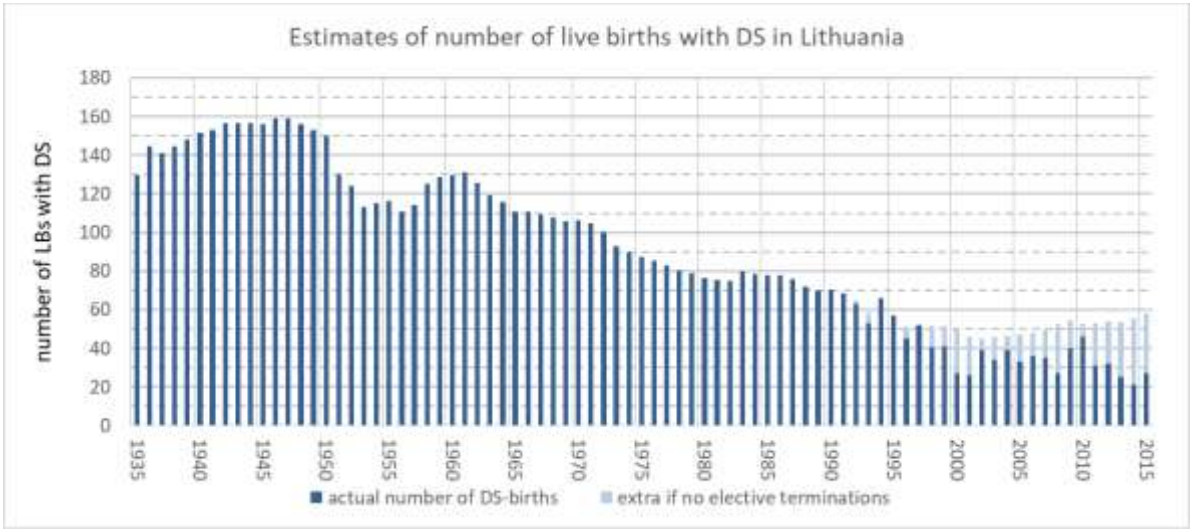


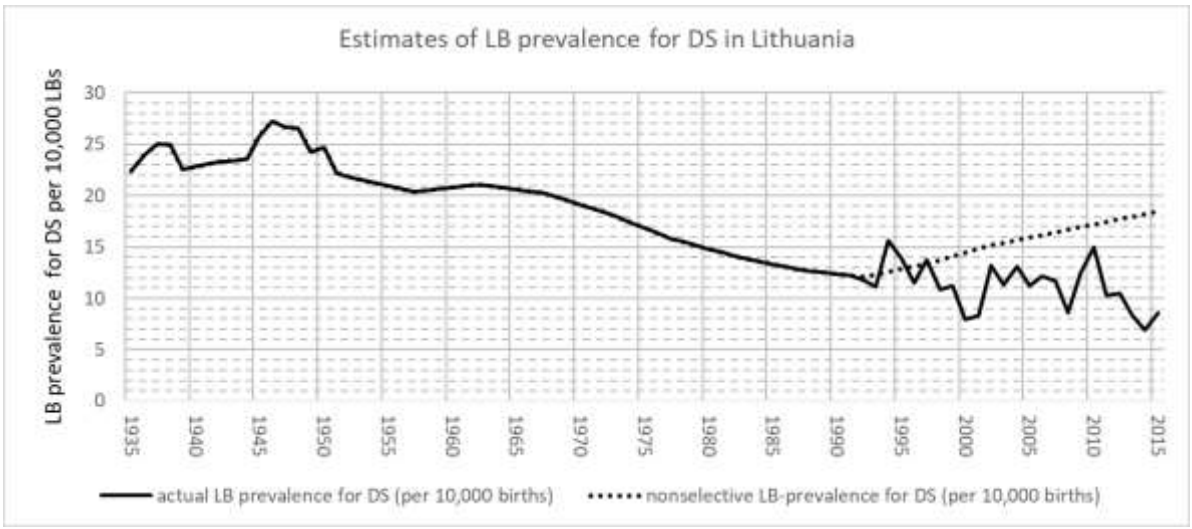


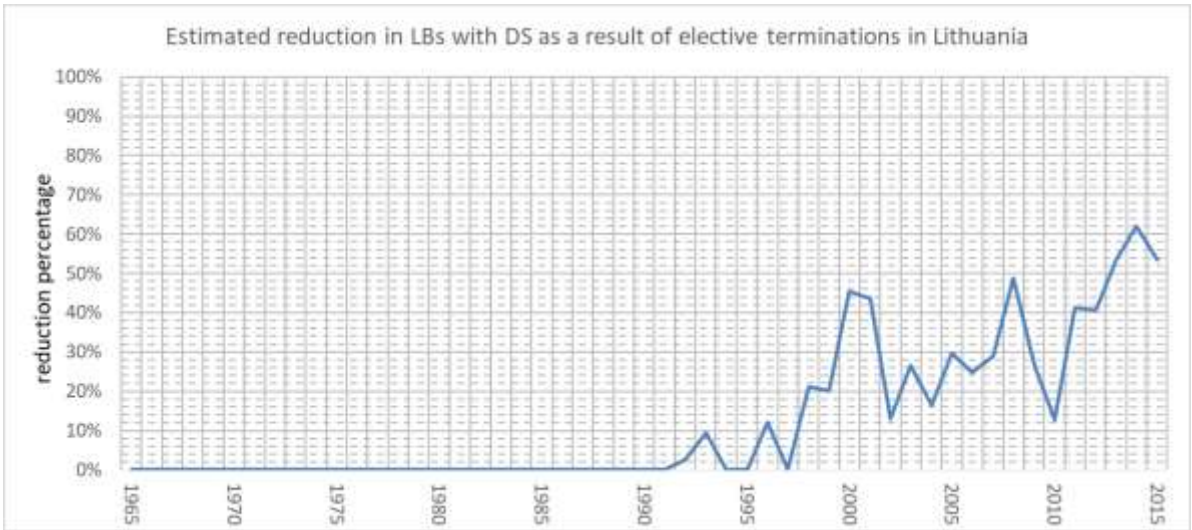

Estimated people with DS in Latvia, 1950-2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Latvia by age group, as of 2015
model B
model D
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Lithuania

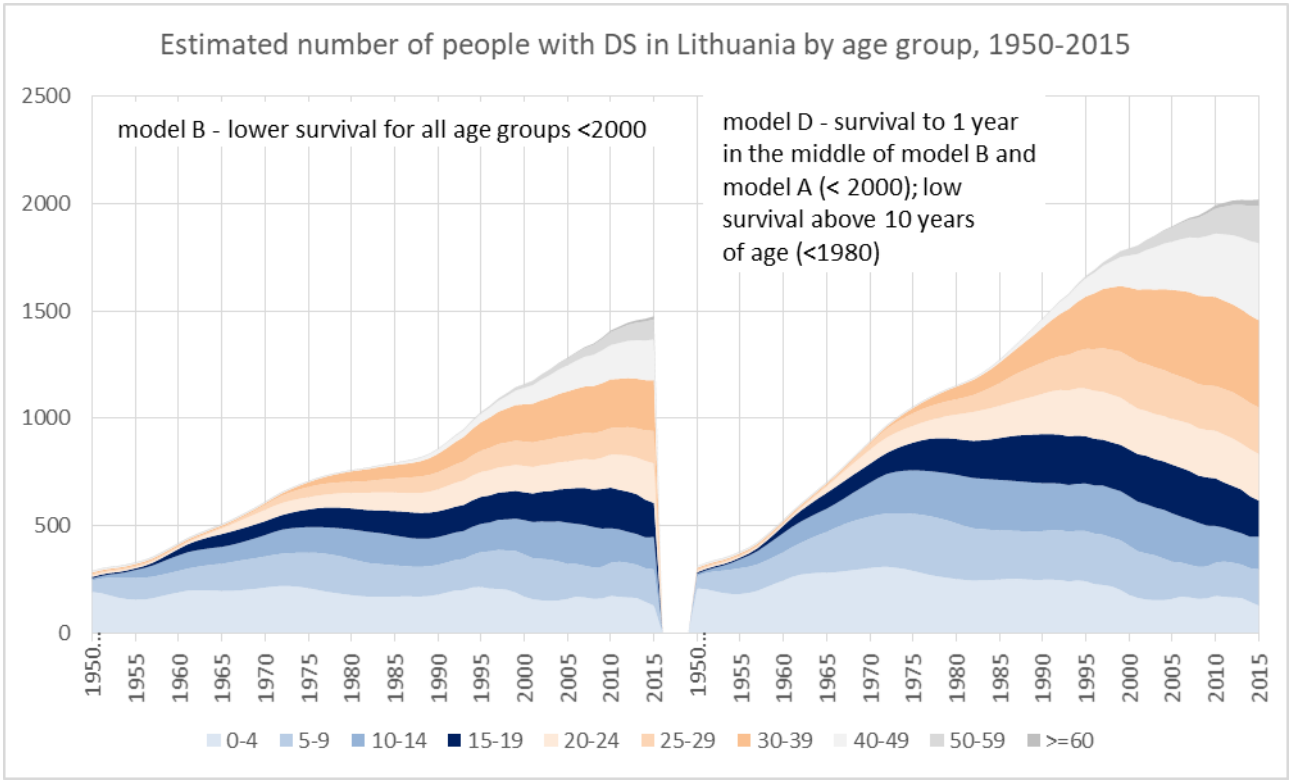


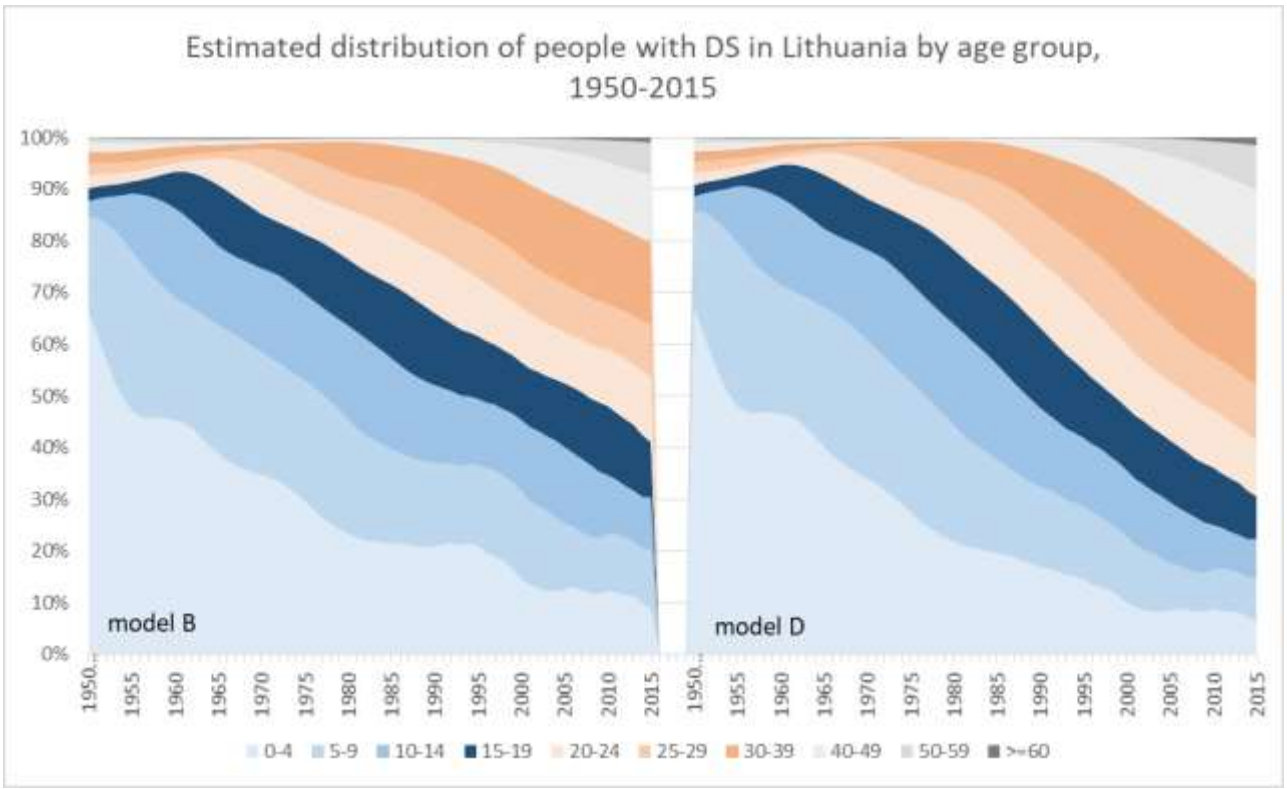


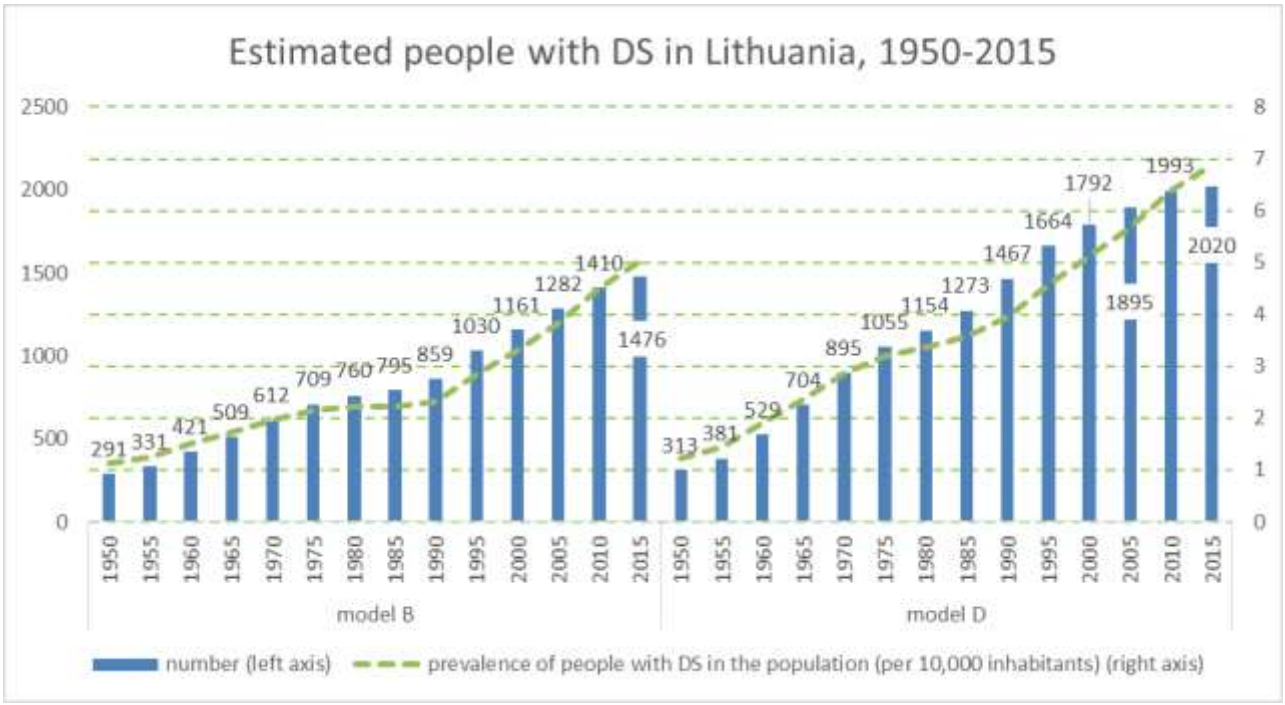


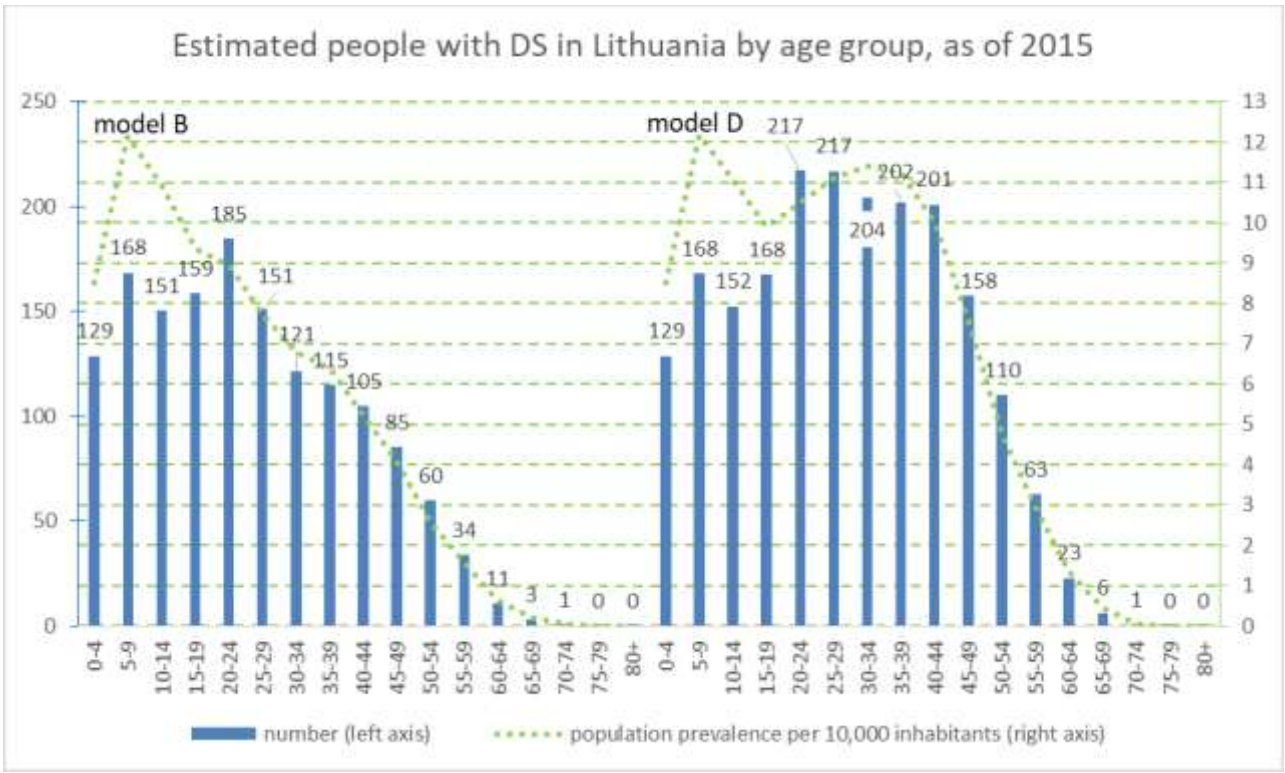
In the graph, negative reduction percentages (if nonselective prevalence is smaller than actual prevalence) have been set at zero after 1991. This is the case for 1994 (with a reduction of -24%), 1995 (-8%), and 1997 (-3%). This can be a result of some random fluctuation in a relatively small population.

Model A projects 2,754 people with DS alive in 2015, which corresponds to a population prevalence of 9.4 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 2,501 (8.5 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Lithuania, Model D seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics for 2005–2015 (see S5C).

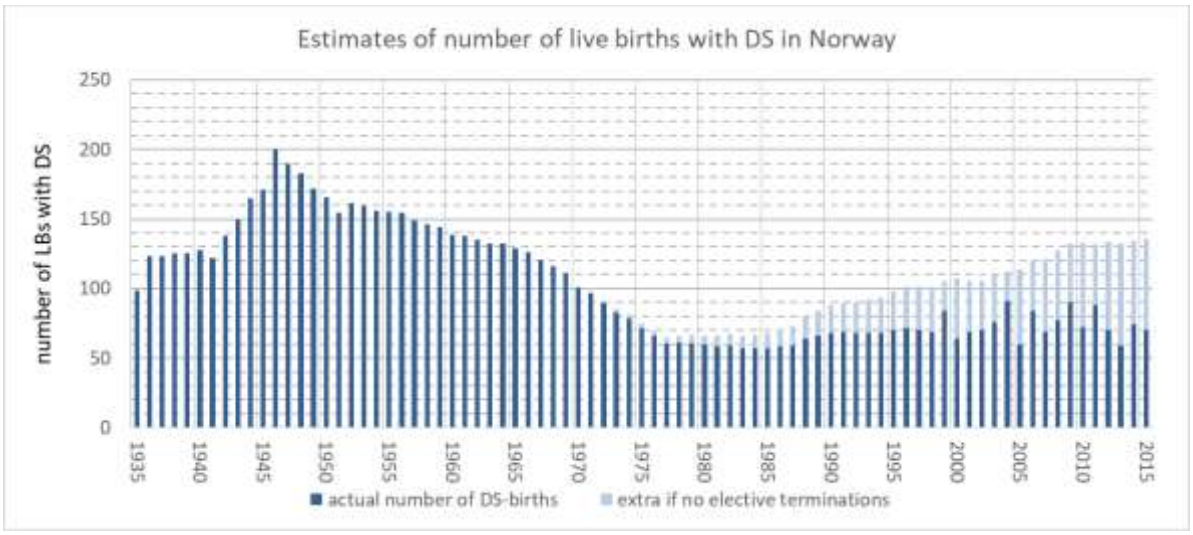


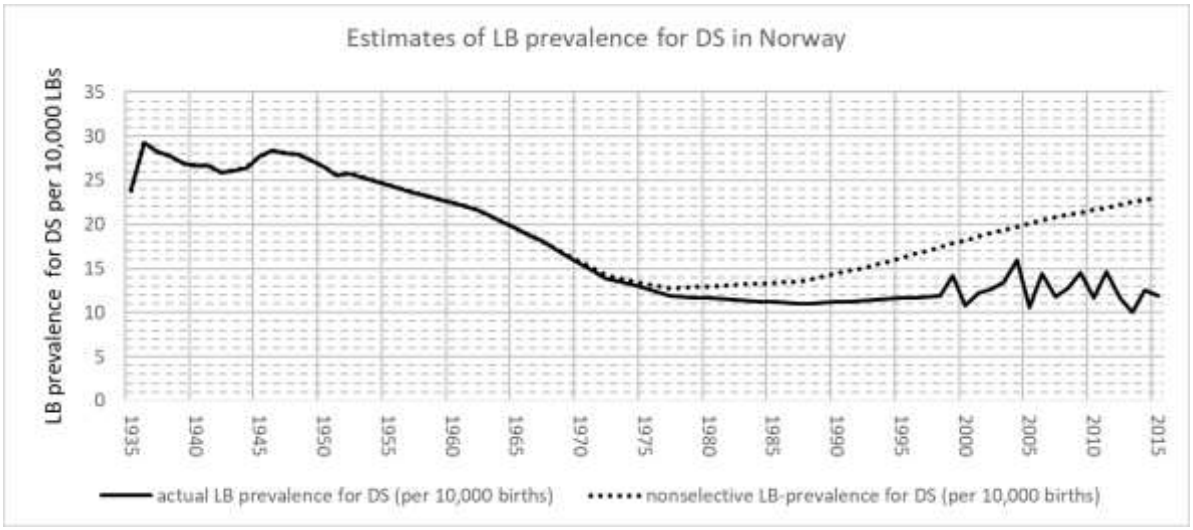


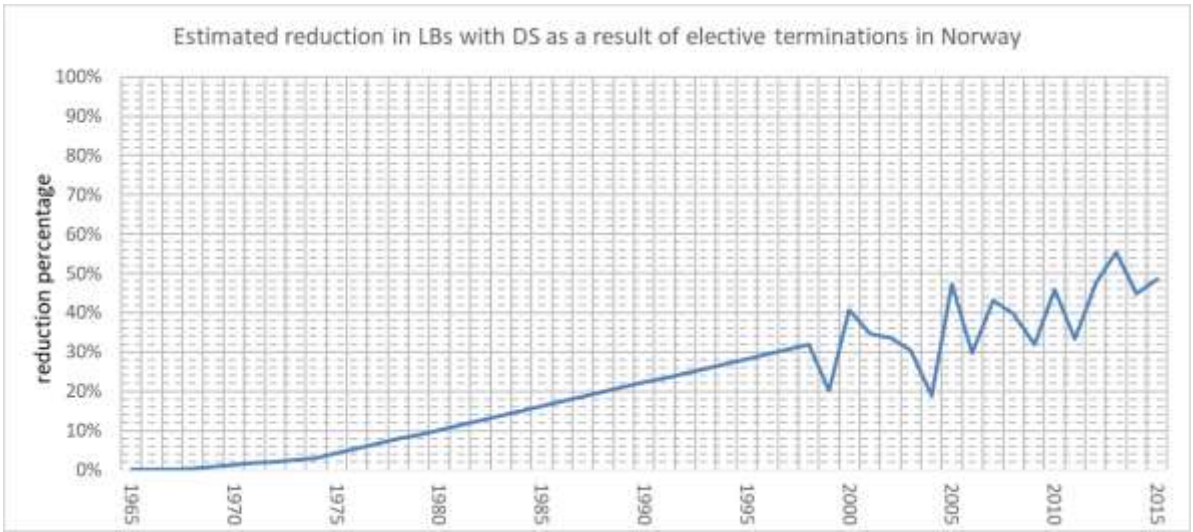

Estimated people with DS in Lithuania, 1950-2015
2500
2000
1500
1000
500
0
8
7
6
5
4
3
2
1
0
291 331 421 509 612 709 760 795 859 1030 1161 1282 1410 1476
313 381 529 704 895 1055 1154 1273 1467 1664 1792 1895 1993 2020
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

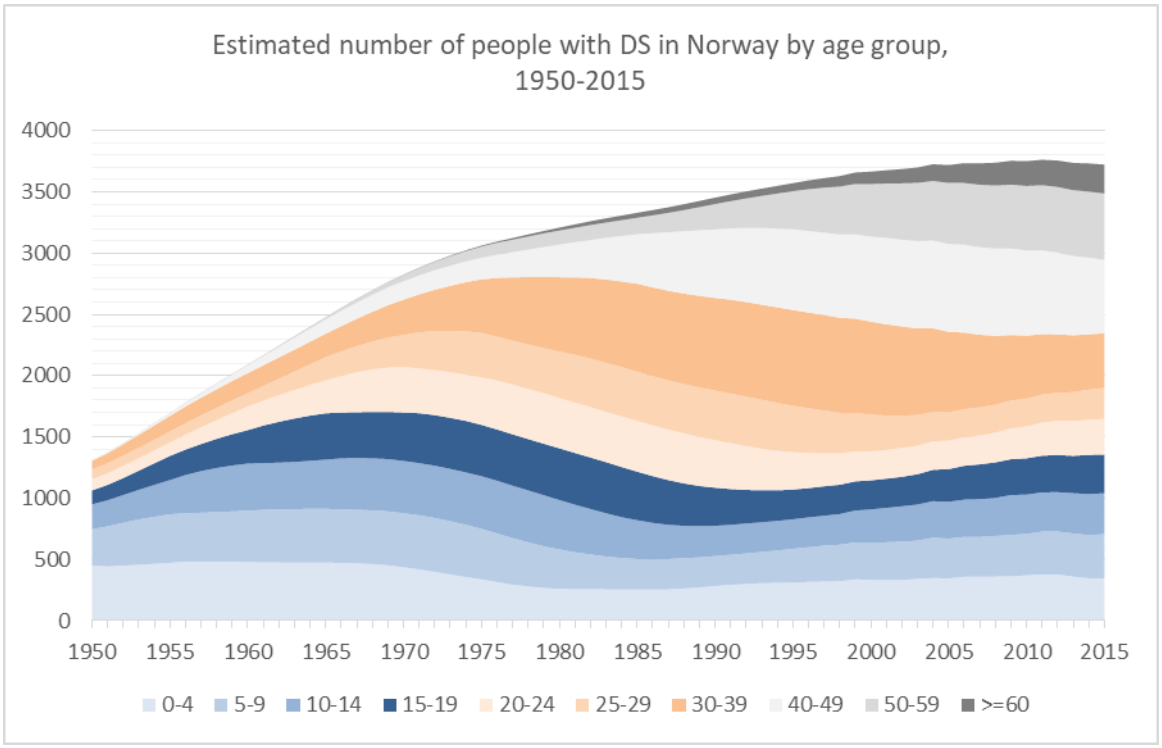

Estimated people with DS in Lithuania by age group, as of 2015
model B
model D
250
200
150
100
50
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
129 168 151 159 185 151 121 115 105 85 60 34 11 3 1 0 0
129 168 152 168 217 217 204 202 201 158 110 63 23 6 1 0 0
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

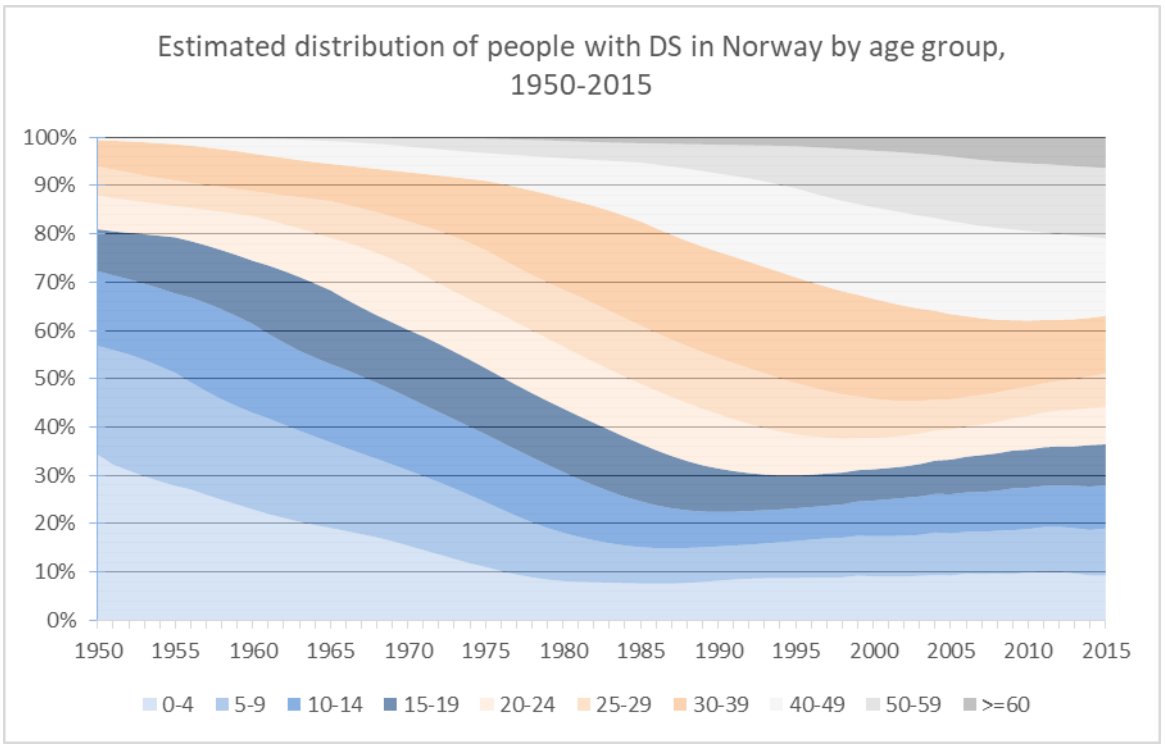
Norway

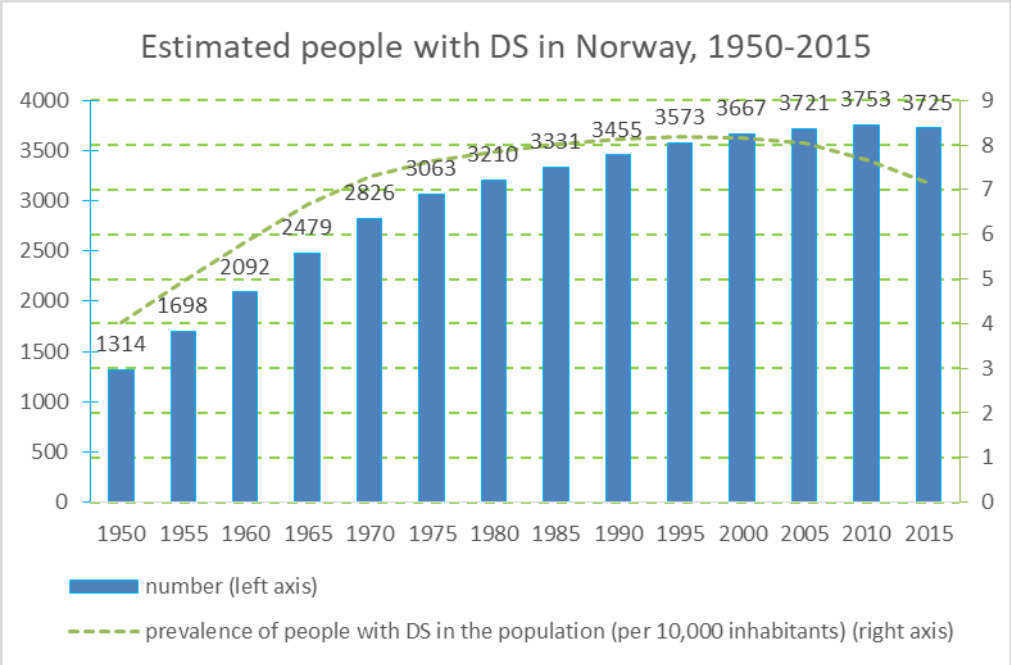

Estimates of number of live births with DS in Norway
number of LBs with DS
250
200
150
100
50
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

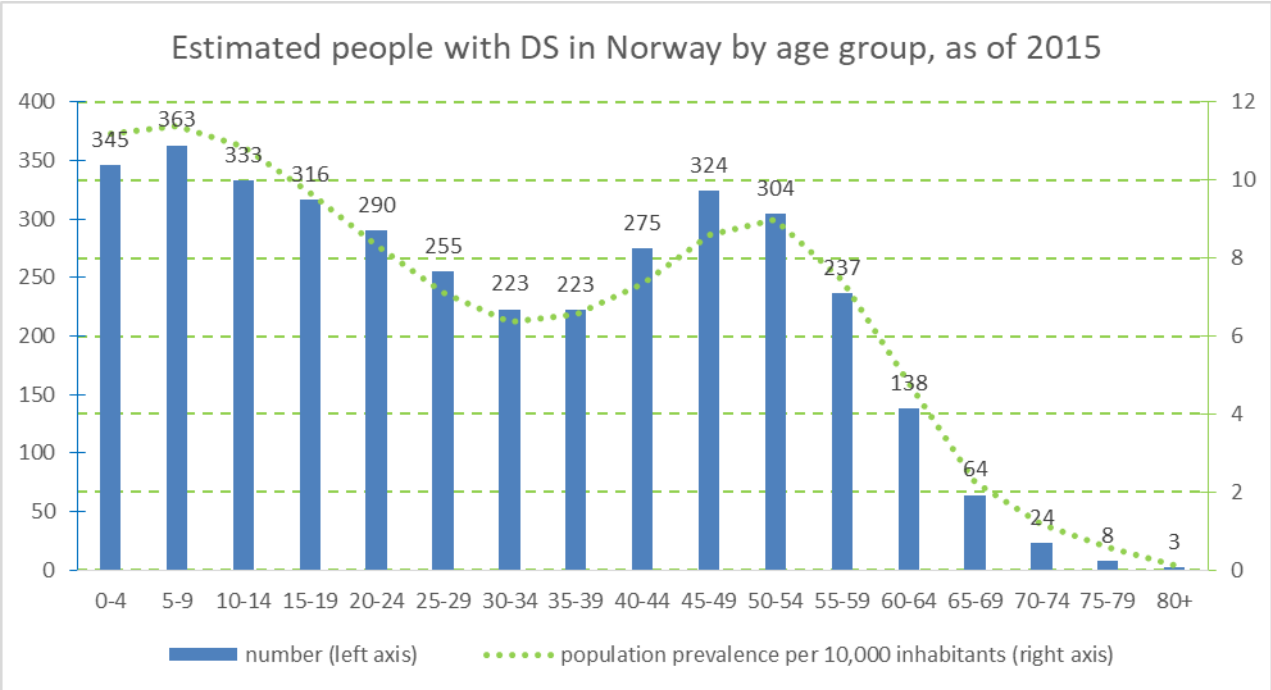

Estimates of LB prevalence for DS in Norway
LB prevalence for DS per 10,000 LBs
35
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Norway
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

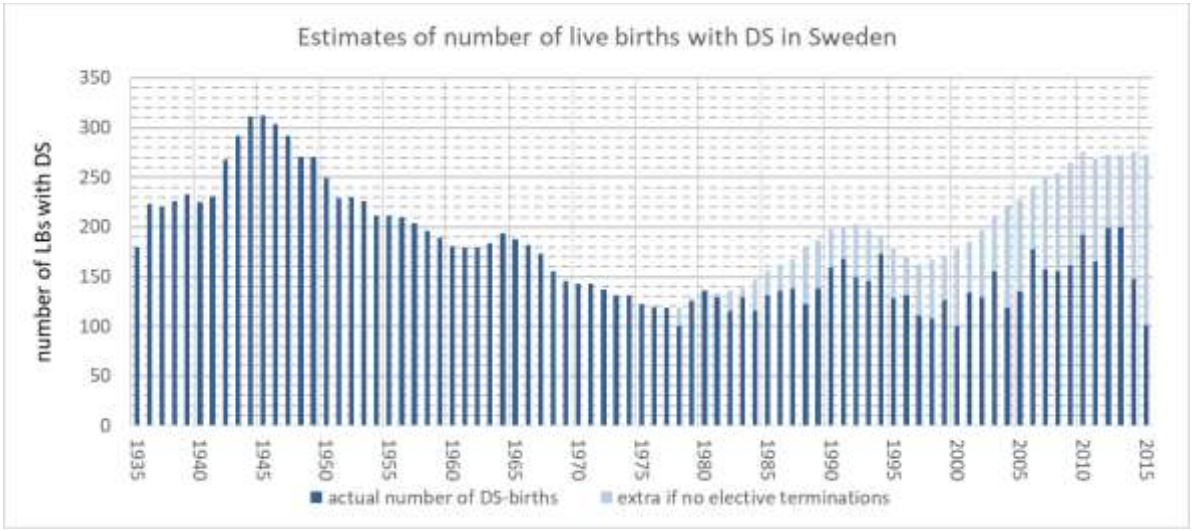

Estimated number of people with DS in Norway by age group, 1950-2015
4000
3500
3000
2500
2000
1500
1000
500
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

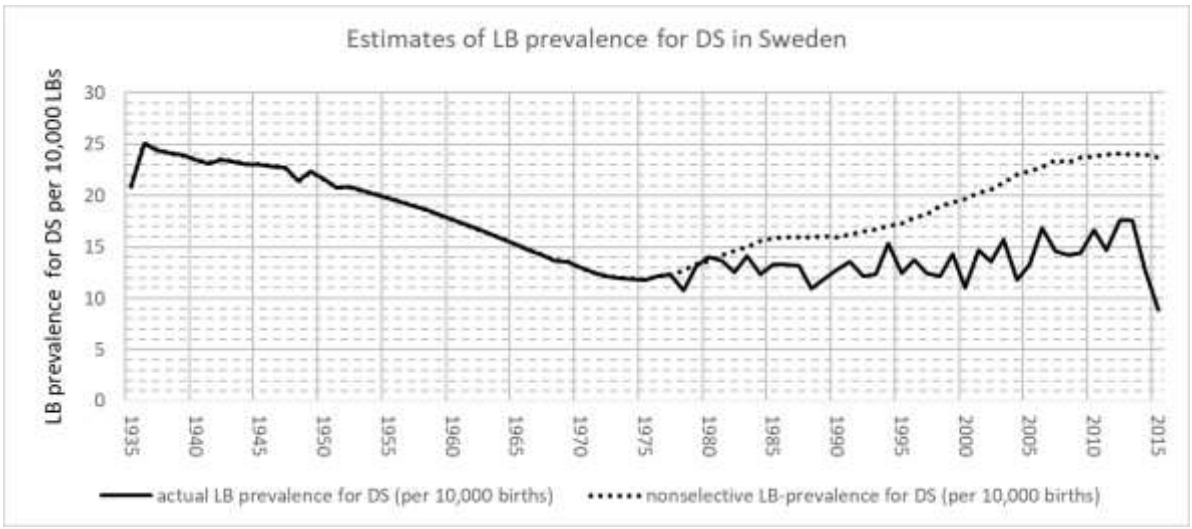

Estimated distribution of people with DS in Norway by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

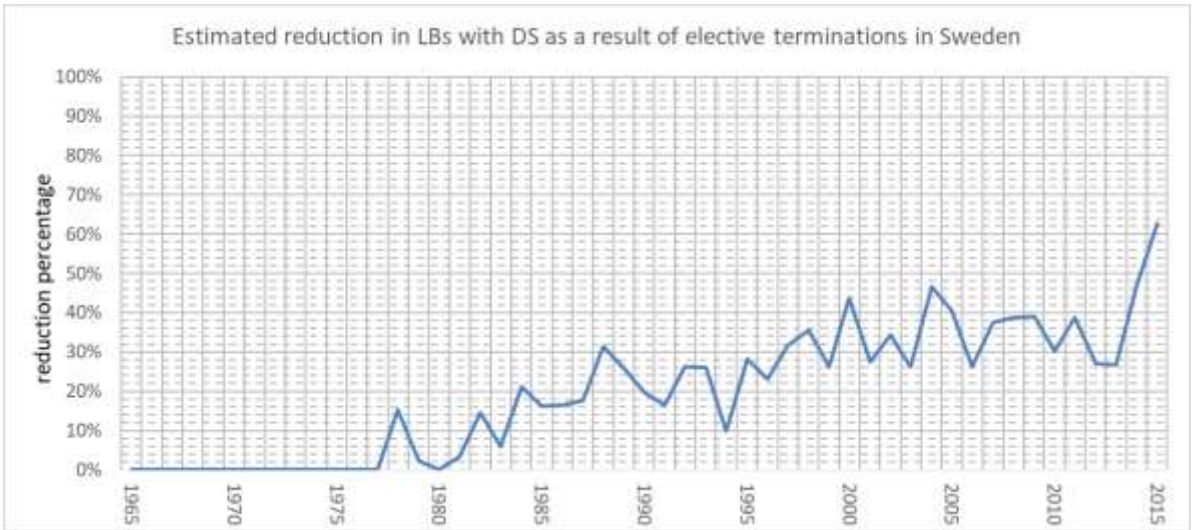

Estimated people with DS in Norway, 1950-2015
4000
3500
3000
2500
2000
1500
1000
500
0
9
8
7
6
5
4
3
2
1
0
1314
1698
2092
2479
2826
3063
3210
3331
3455
3573
3667
3721
3753
3725
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Norway by age group, as of 2015
400
350
300
250
200
150
100
50
0
12
10
8
6
4
2
0
345
363
333
316
290
255
223
223
275
324
304
237
138
64
24
8
3
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

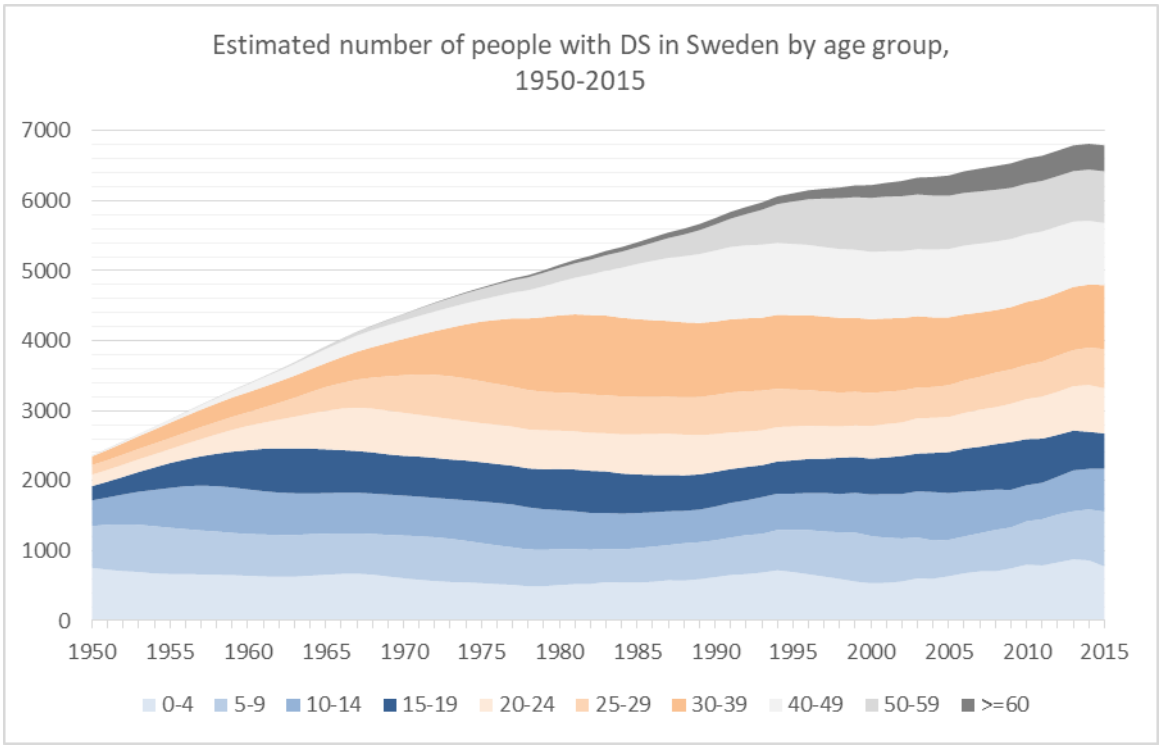
Sweden

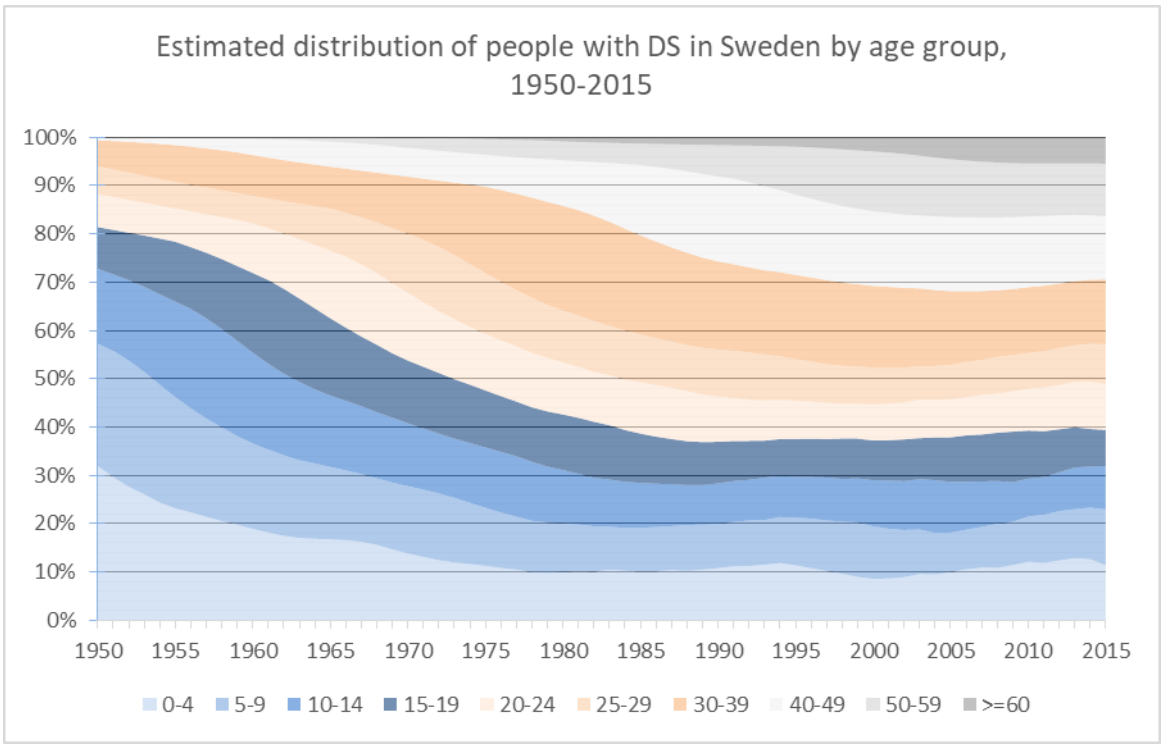


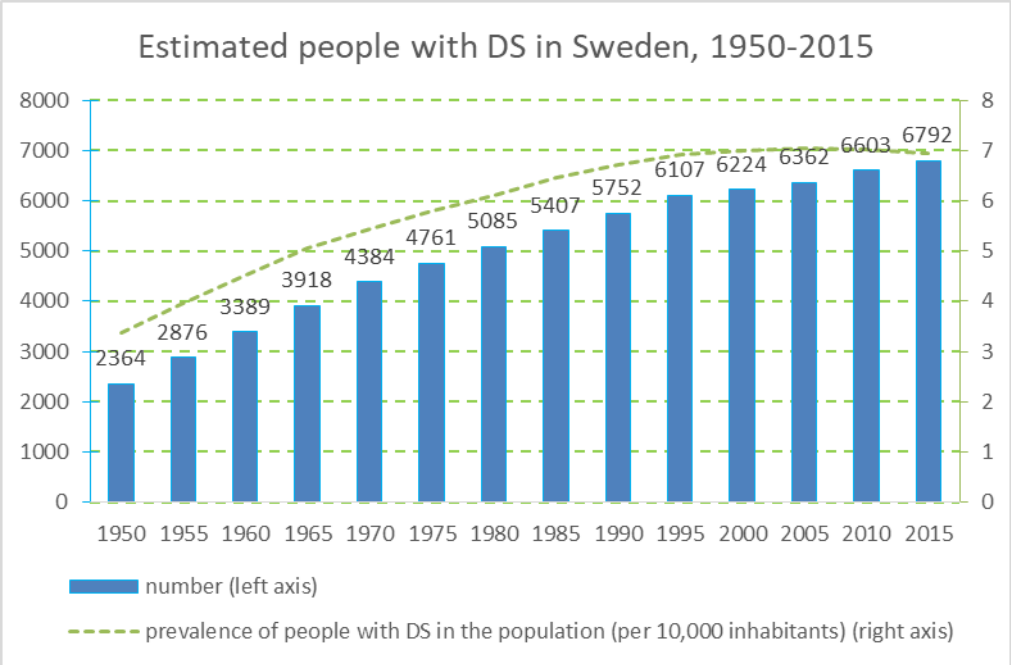


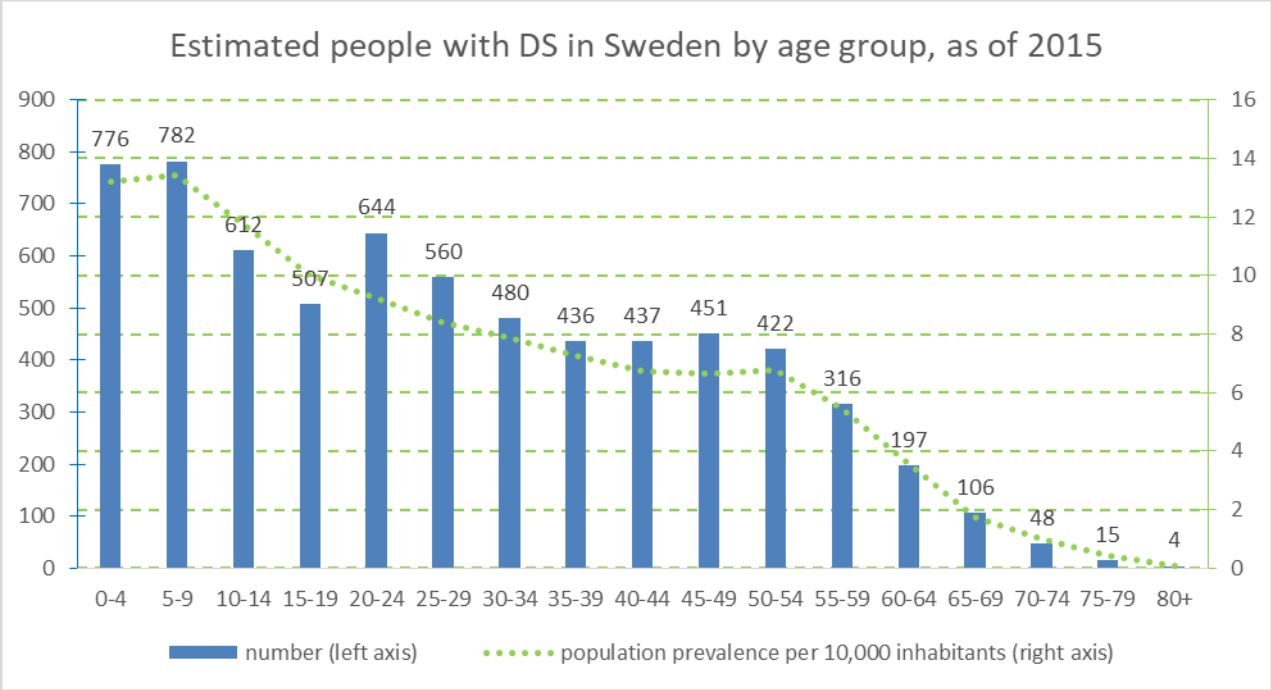


In the graph, negative reduction percentages (if nonselective prevalence is smaller than actual prevalence) have been set at zero after 1977. This is the case for 1980 (with a reduction of -1%). This can be a result of some random fluctuation in a relatively small population.

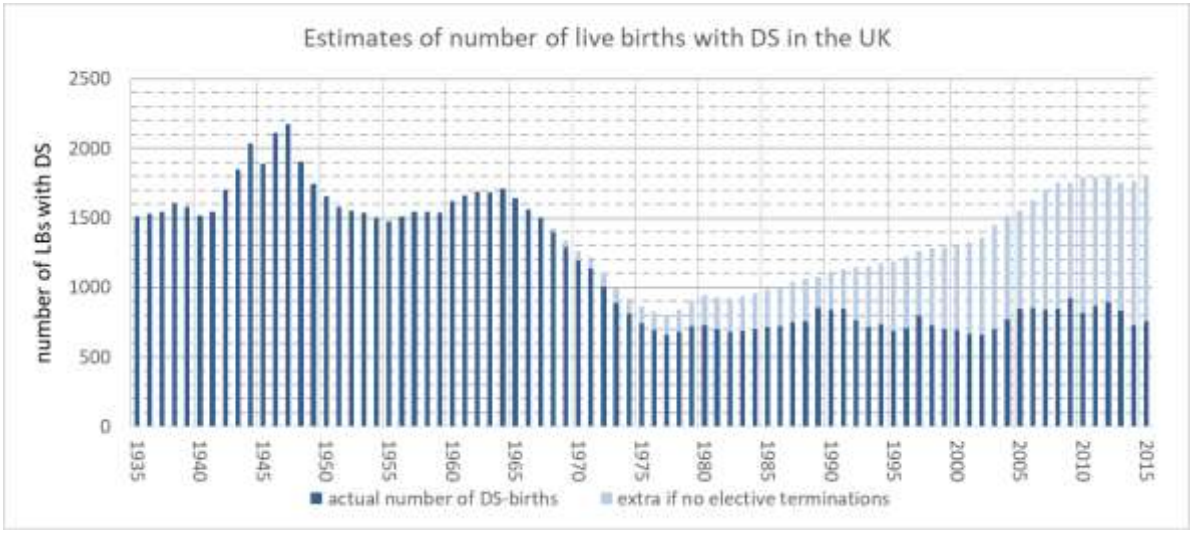

Estimated number of people with DS in Sweden by age group, 1950-2015
7000
6000
5000
4000
3000
2000
1000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

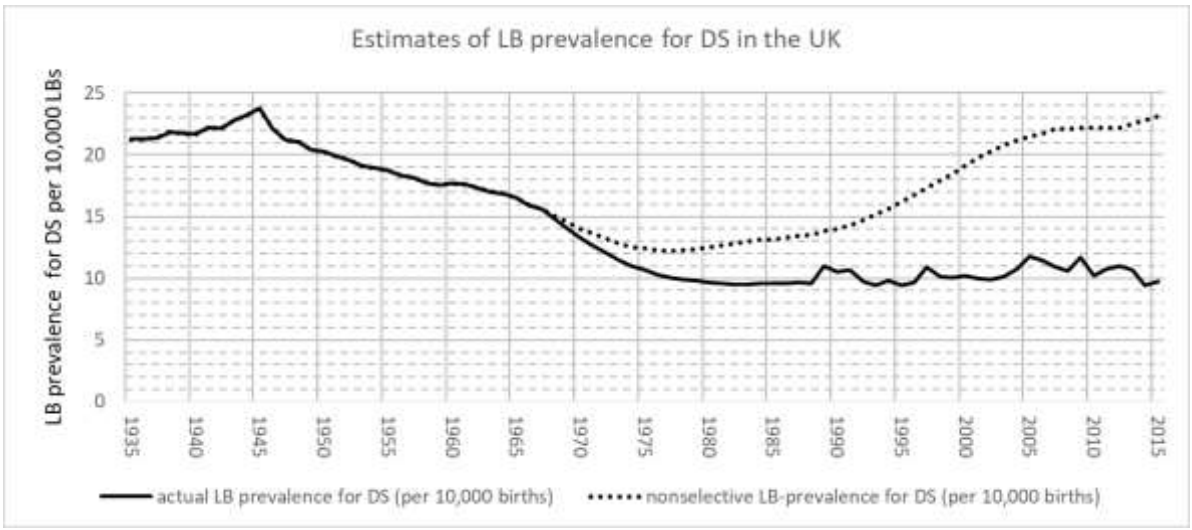

Estimated distribution of people with DS in Sweden by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

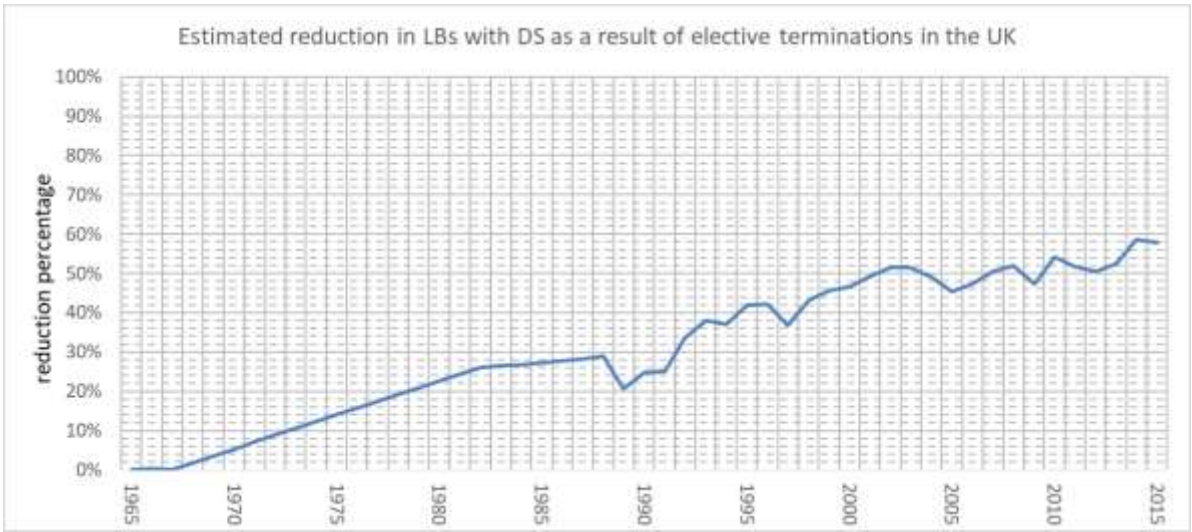

Estimated people with DS in Sweden, 1950-2015
8000
7000
6000
5000
4000
3000
2000
1000
0
8
7
6
5
4
3
2
1
0
2364
2876
3389
3918
4384
4761
5085
5407
5752
6107
6224
6362
6603
6792
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

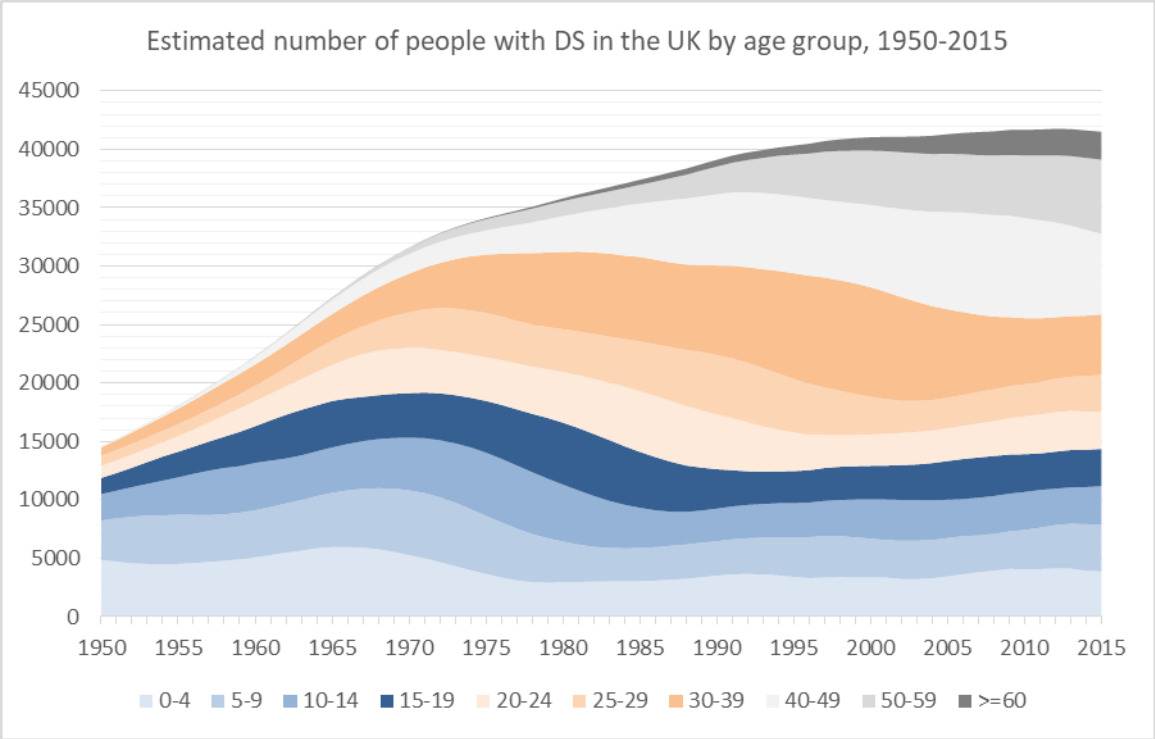

Estimated people with DS in Sweden by age group, as of 2015
900
800
700
600
500
400
300
200
100
0
16
14
12
10
8
6
4
2
0
776
782
612
507
644
560
480
436
437
451
422
316
197
106
48
15
4
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

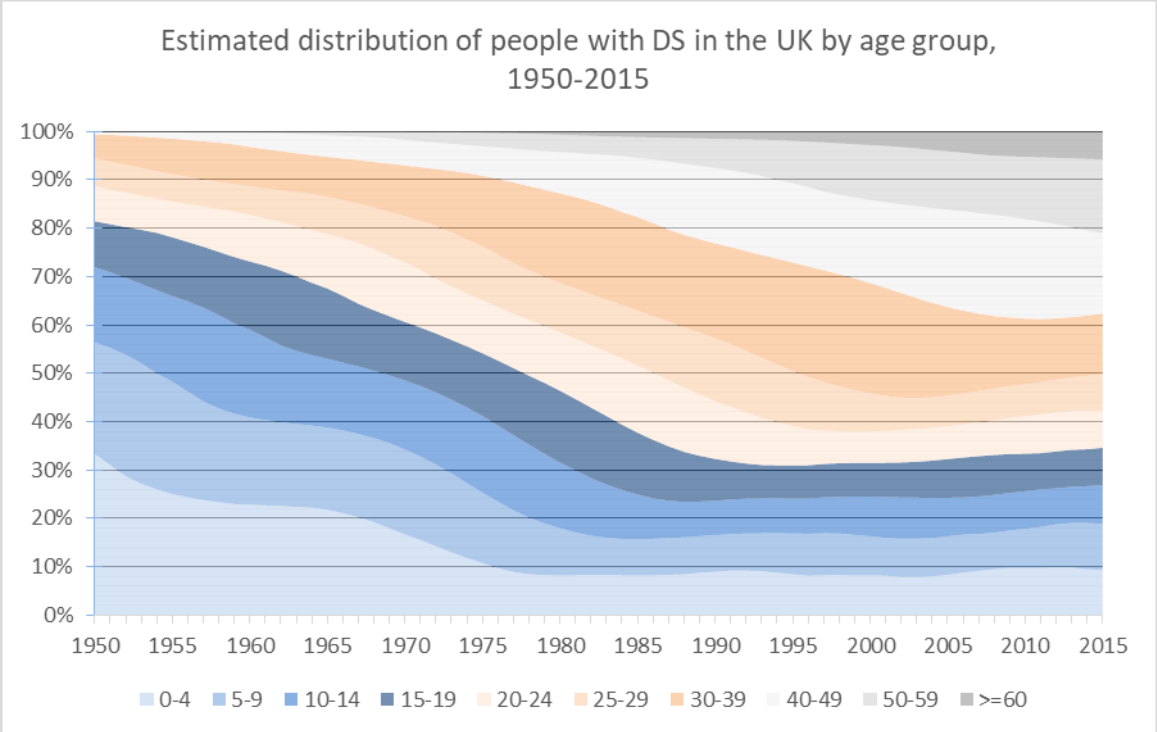
United Kingdom

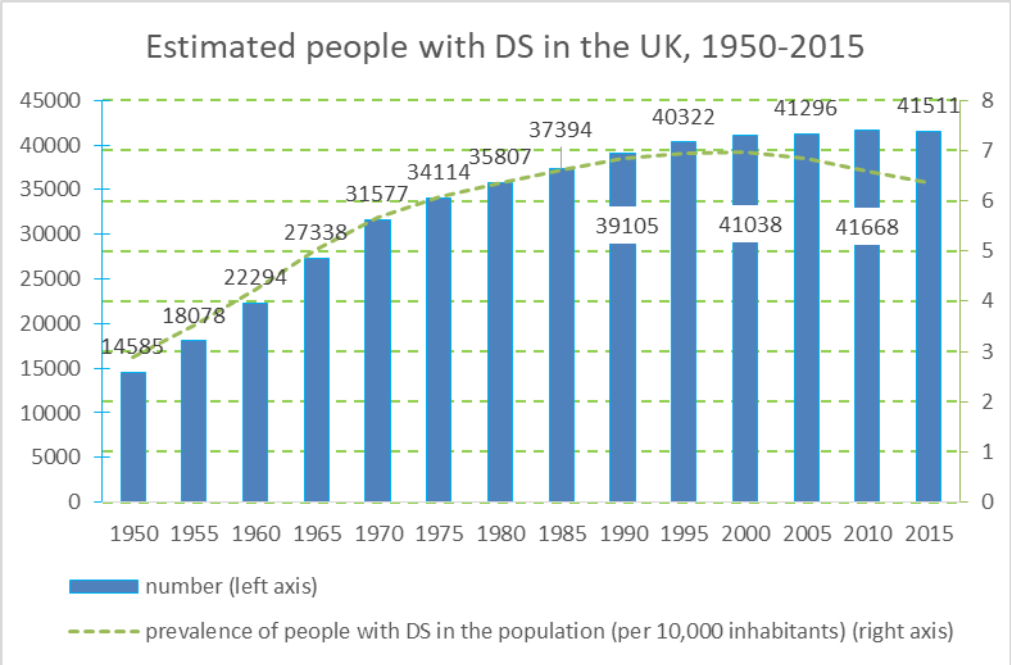


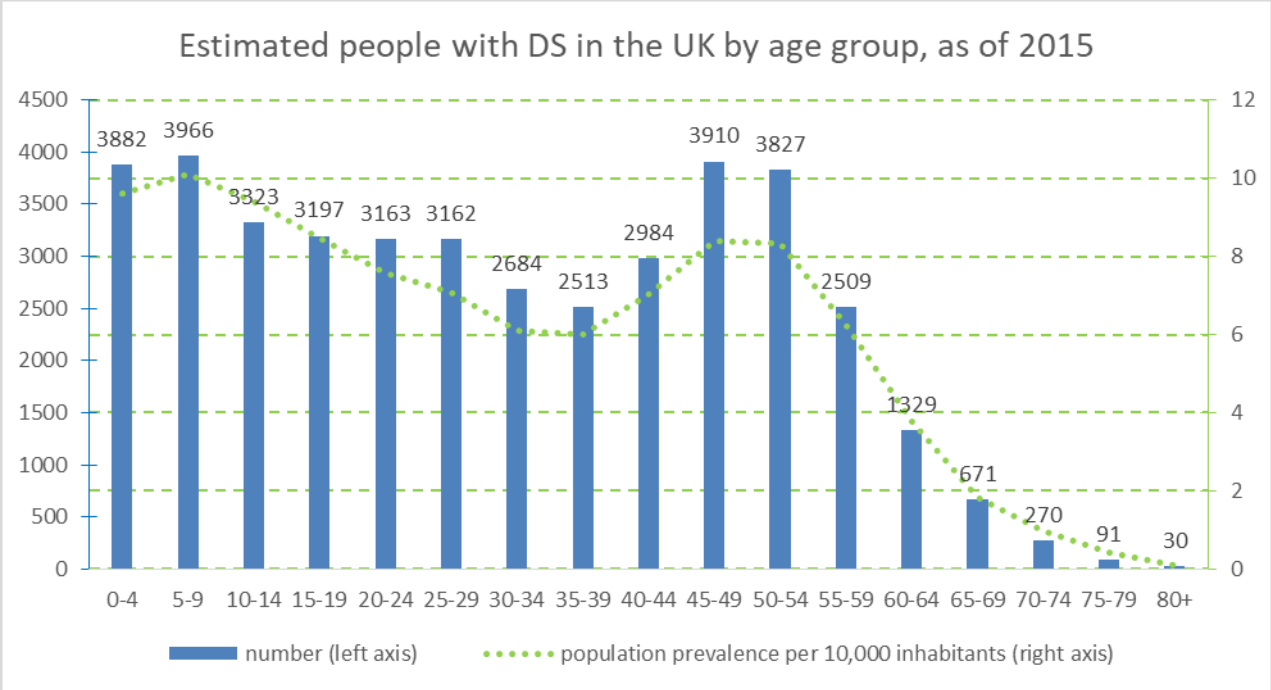





Estimated number of people with DS in the UK by age group, 1950-2015
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

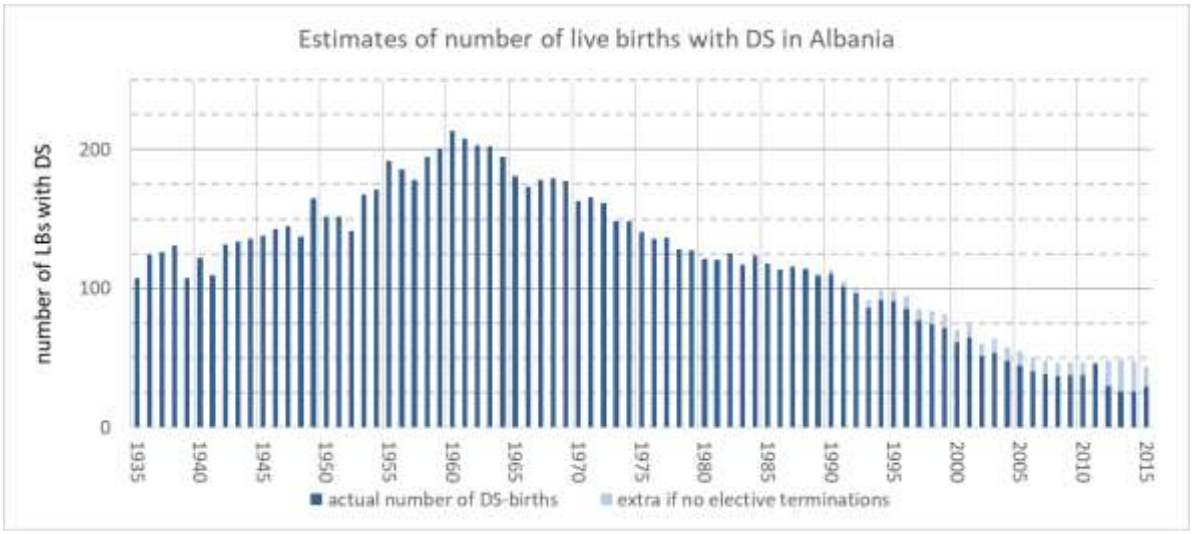

Estimated distribution of people with DS in the UK by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

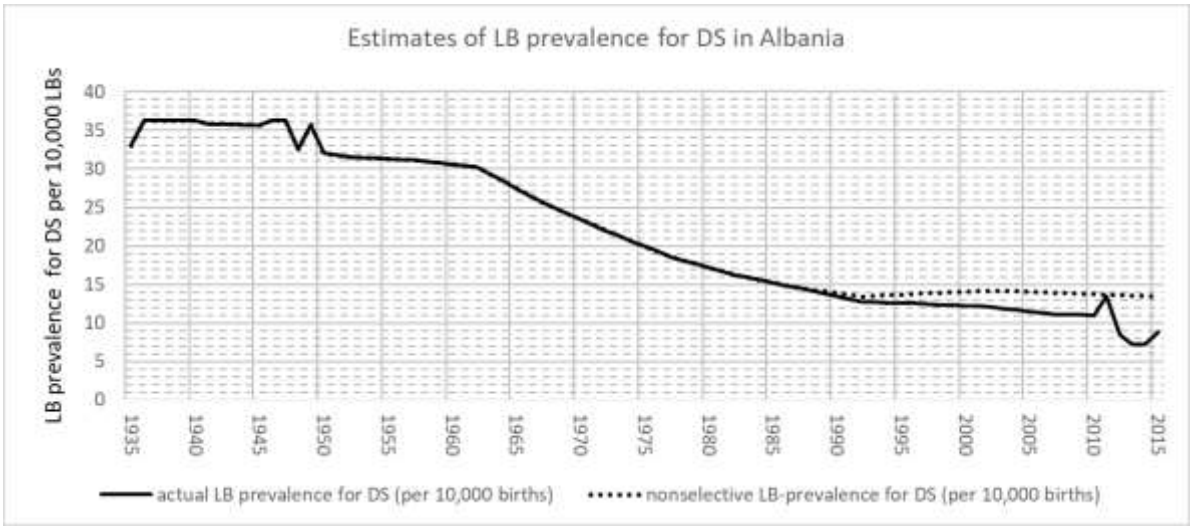

Estimated people with DS in the UK, 1950-2015
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
8
7
6
5
4
3
2
1
0
14585
18078
22294
27338
31577
34114
35807
37394
39105
40322
41038
41296
41668
41511
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

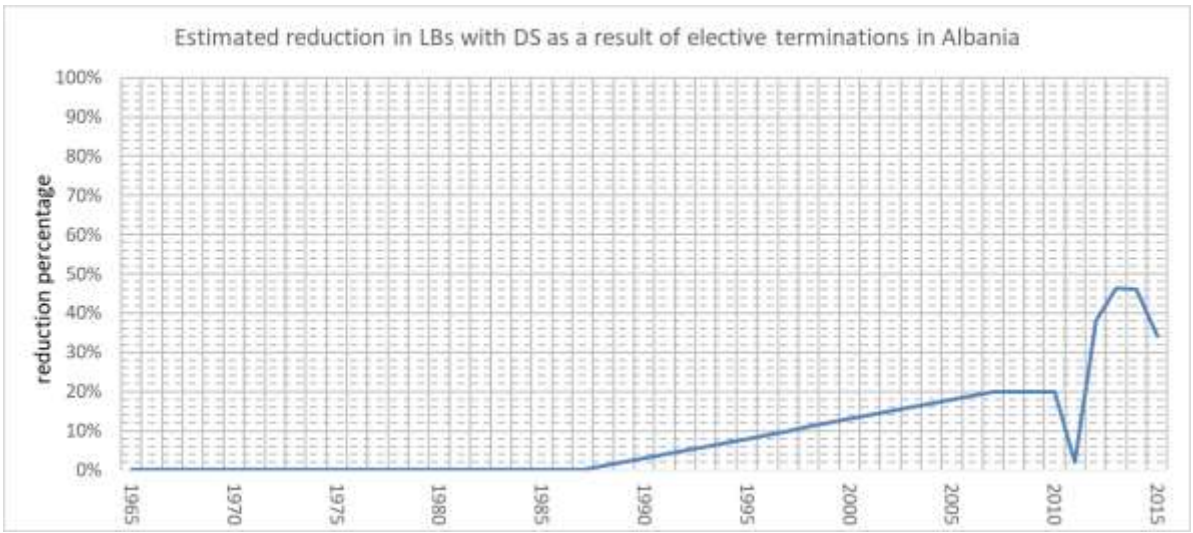

Estimated people with DS in the UK by age group, as of 2015
4500
4000
3500
3000
2500
2000
1500
1000
500
0
12
10
8
6
4
2
0
3882
3966
3323
3197
3163
3162
2684
2513
2984
3910
3827
2509
1329
671
270
91
30
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Southern Europe

Albania

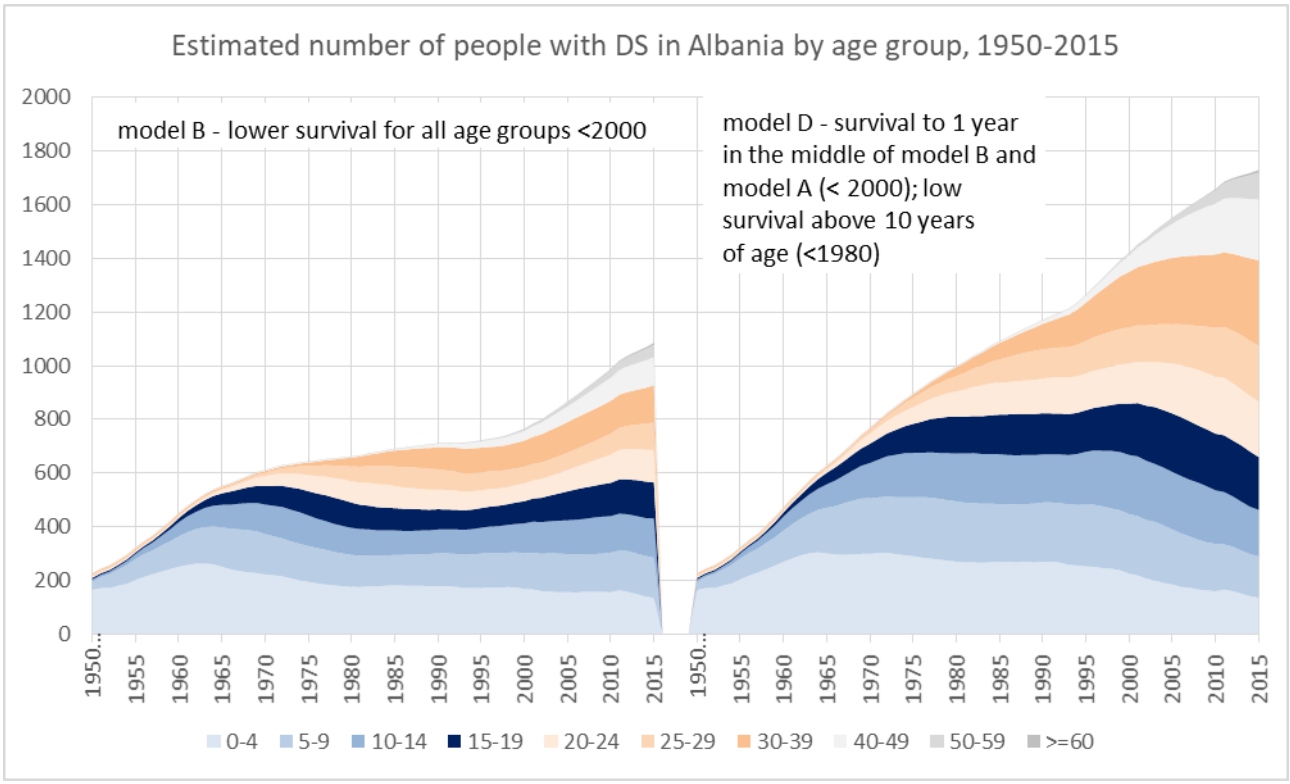


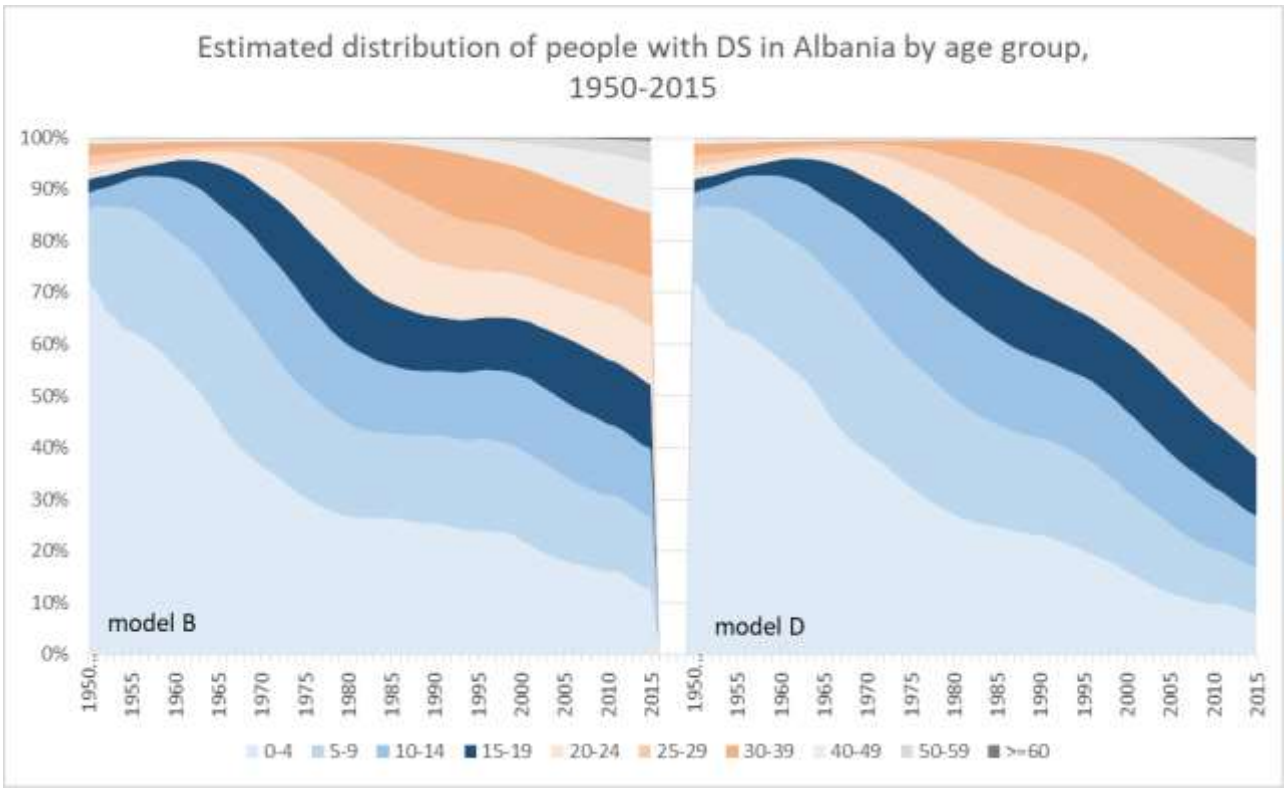


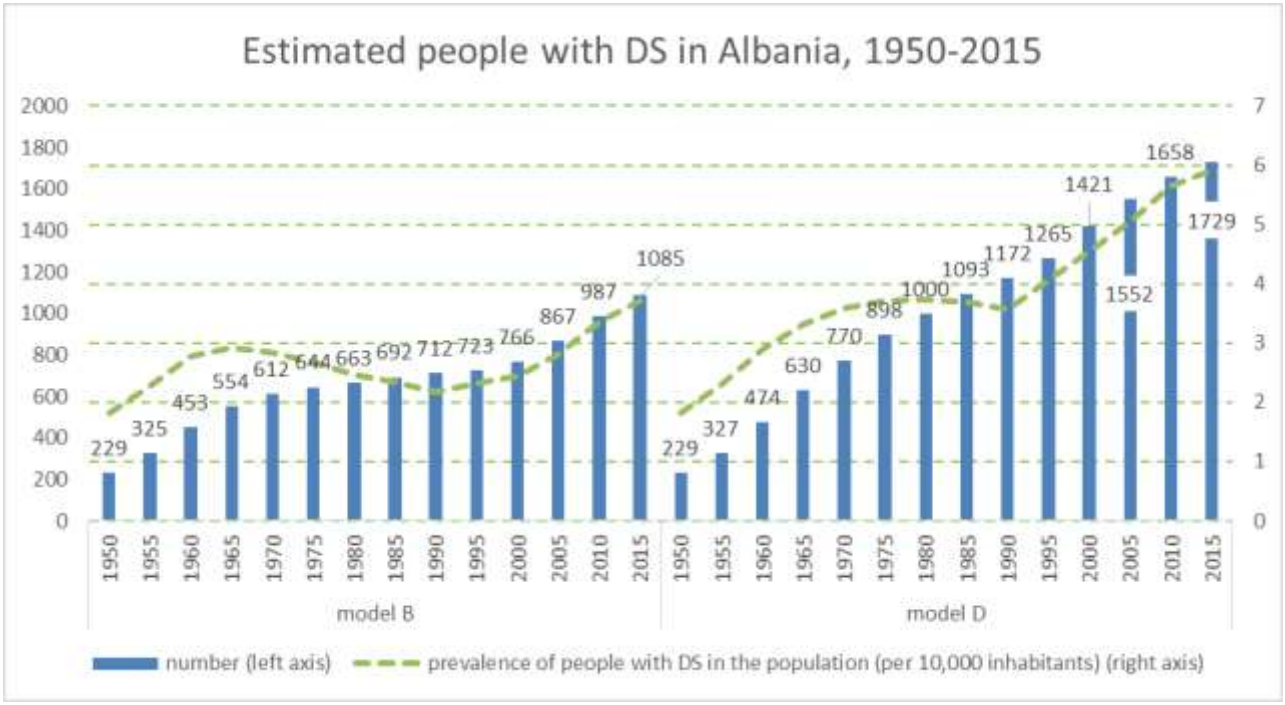


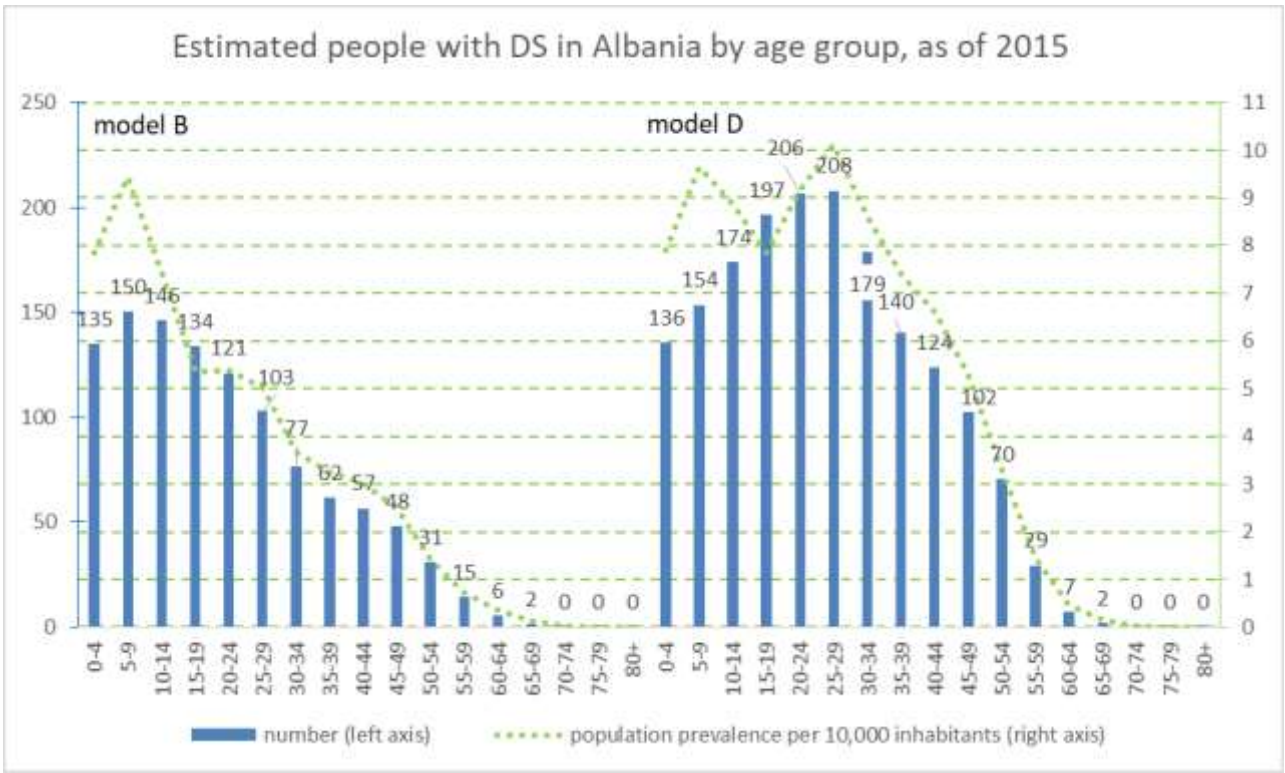
* For 2011–15 reported data were used; before 2011 interpolations (see S1C).

Model A projects 2,693 people with DS alive in 2015, which corresponds to a population prevalence of 9.2 people with DS per 10,000 inhabitants. Model C projects 2,553 (8.7 per 10,000). However, we consider Model B or Model D more likely. Model B fits the data on number of people alive in Albania, as of 2015, as reported by the National Social Service (and corrected for under-ascertainment) (see S5A). However, it is possible that under-ascertainment in the older age groups is larger than in younger people with DS, which would be the case if Model D is correct. For Albania, there is no info on deaths with DS from national statistics.

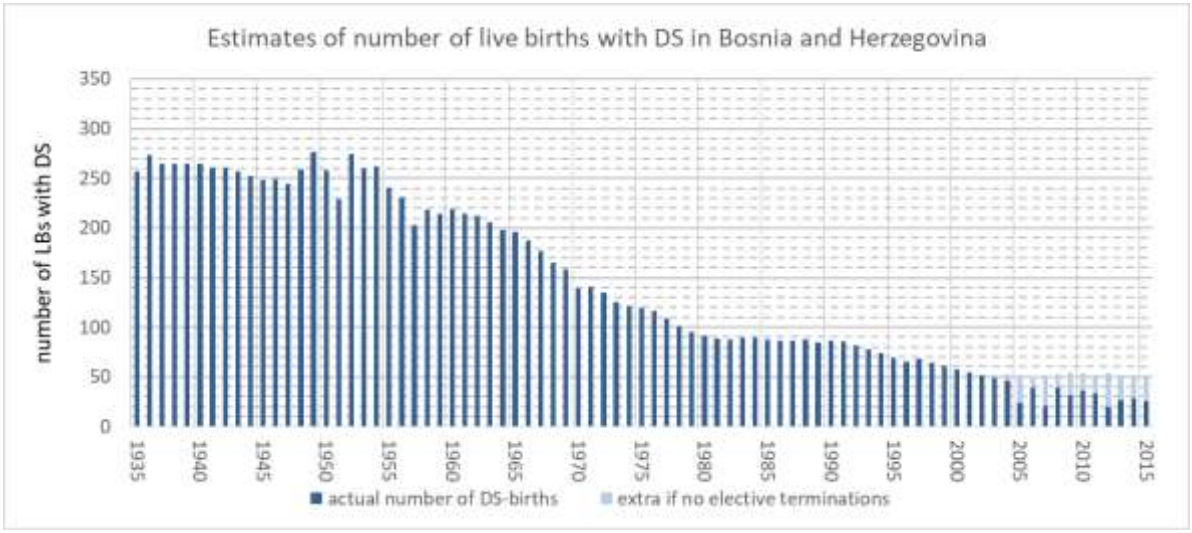


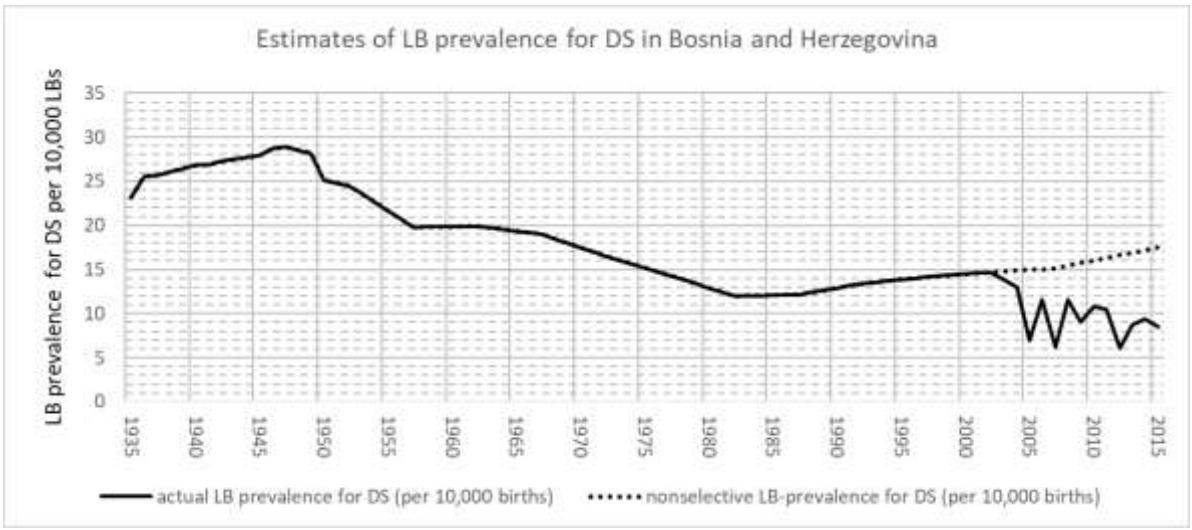


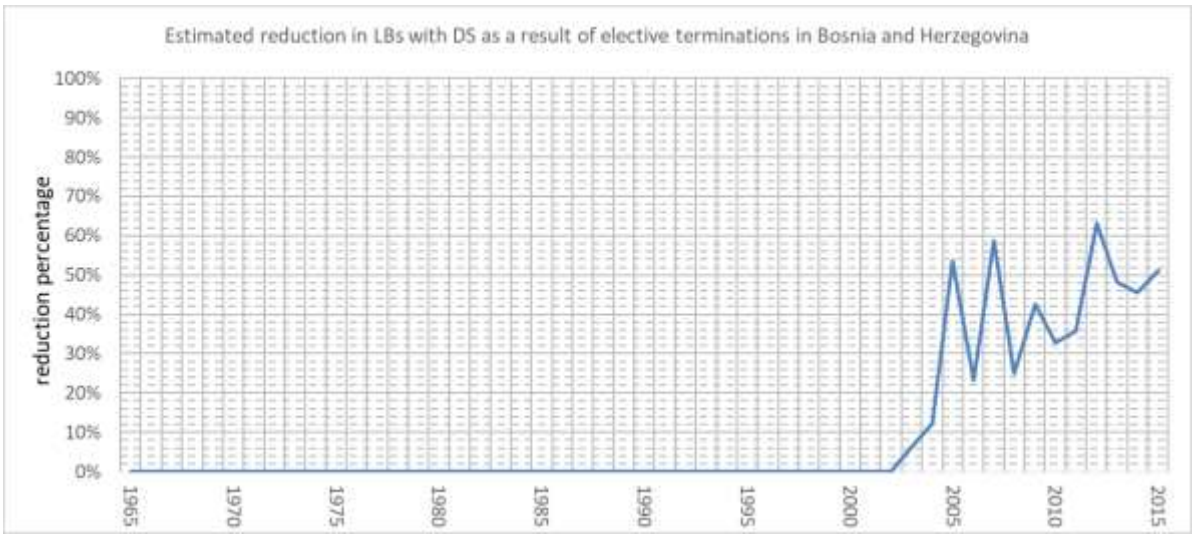

Estimated people with DS in Albania, 1950-2015
2000
1800
1600
1400
1200
1000
800
600
400
200
0
7
6
5
4
3
2
1
0
229 325 453 554 612 644 663 692 712 723 766 867 987 1085
229 327 474 630 770 898 1000 1093 1172 1265 1421 1552 1658 1729
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Albania by age group, as of 2015
250
200
150
100
50
0
11
10
9
8
7
6
5
4
3
2
1
0
model B
model D
135 150 146 134 121 103 77 62 57 48 31 15 6 2 0 0 0
136 154 174 197 206 208 179 140 124 102 70 29 7 2 0 0 0
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

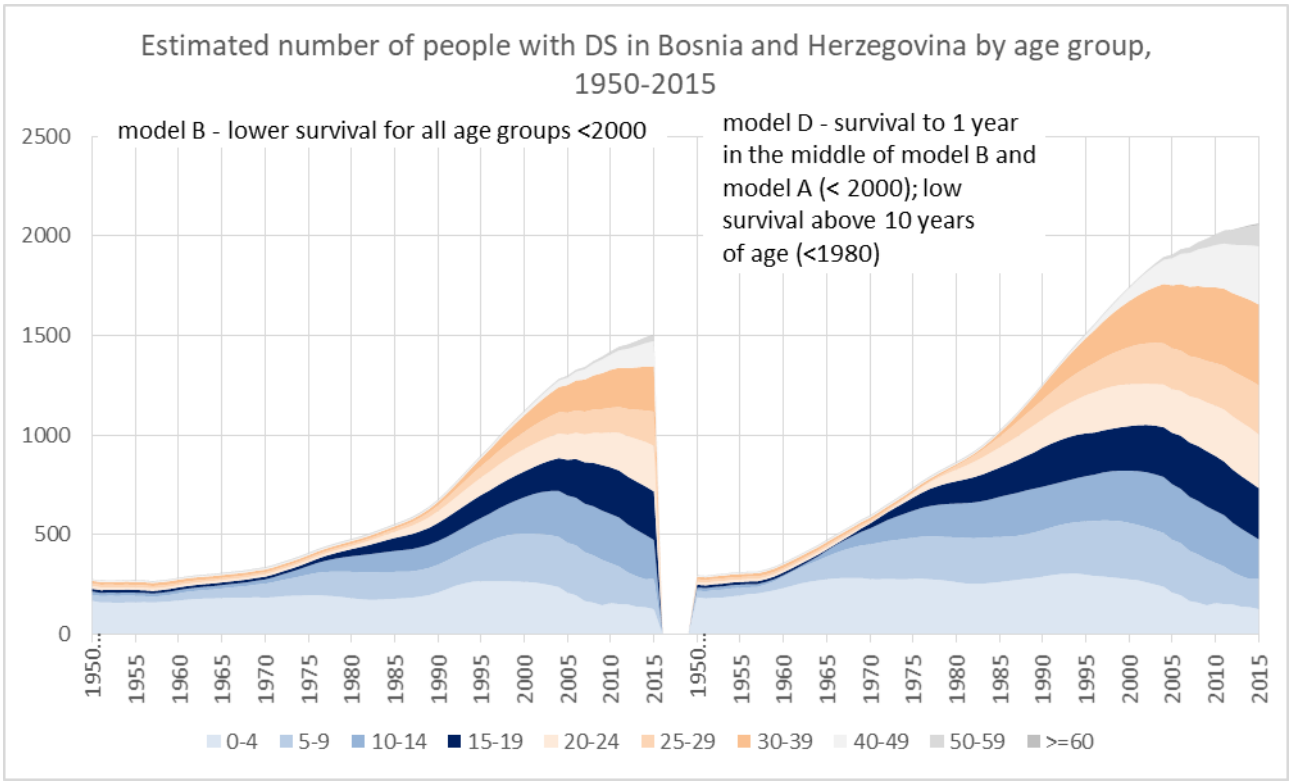
Bosnia and Herzegovina

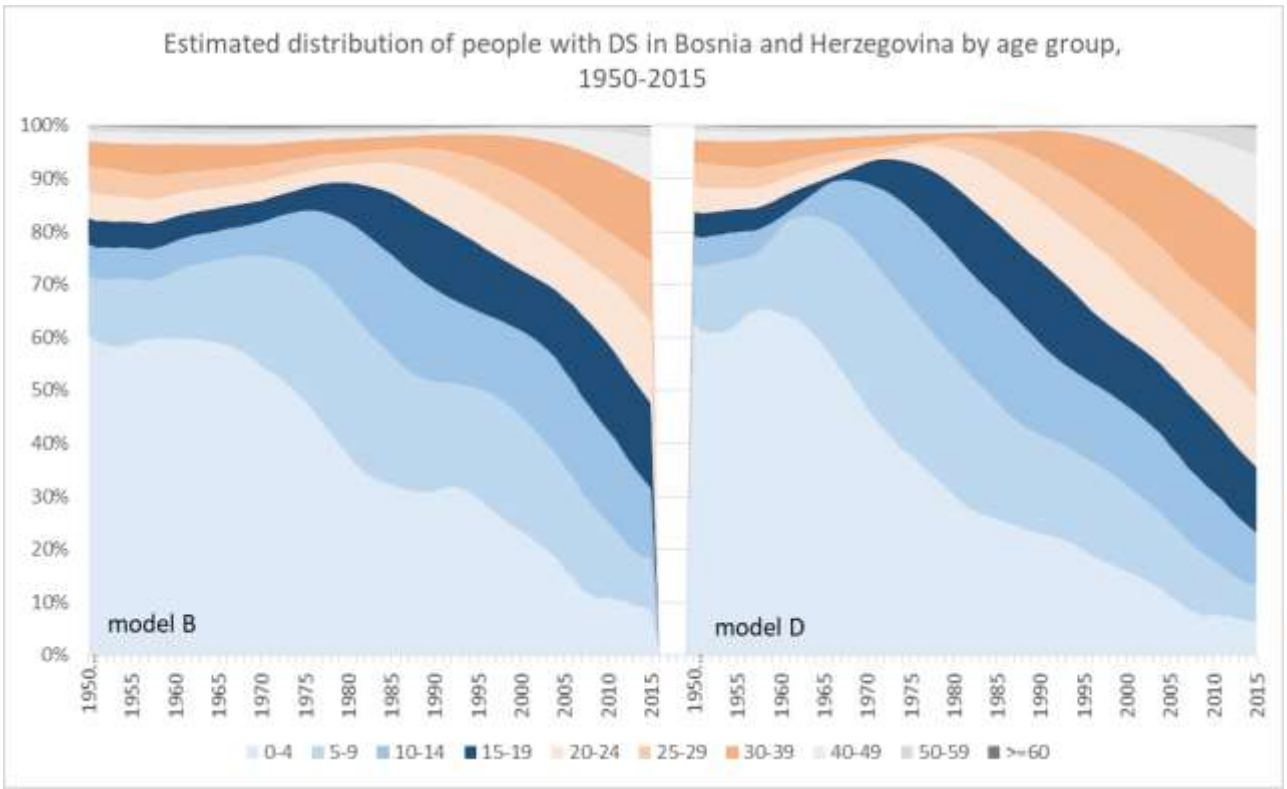


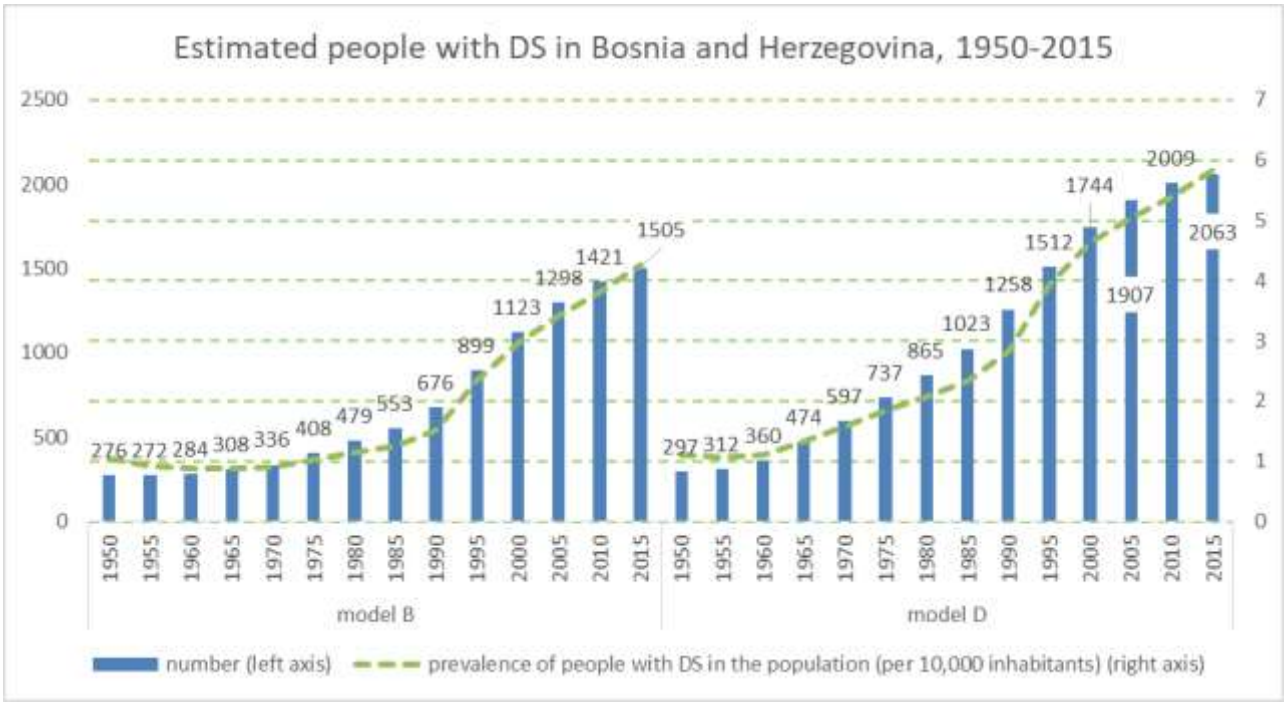


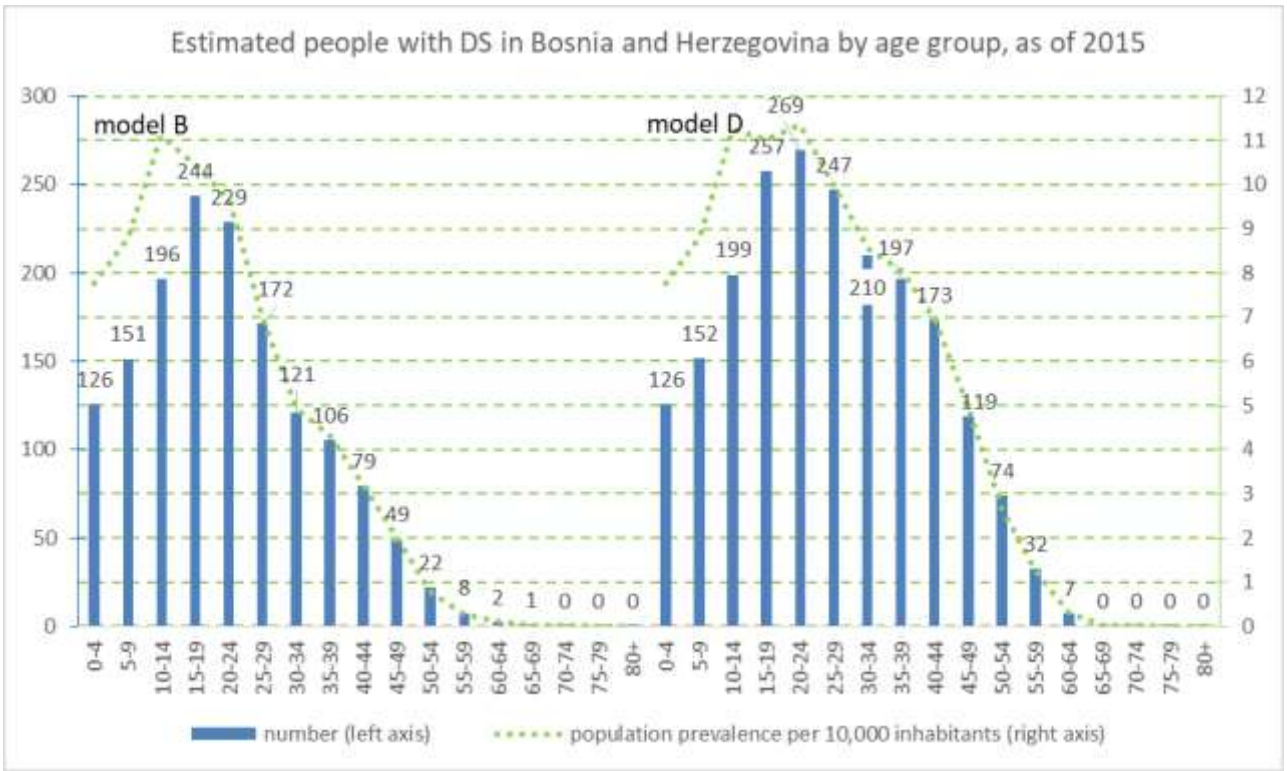


Model A projects 2,732 people with DS alive in 2015, which corresponds to a population prevalence of 7.7 people with DS per 10,000 inhabitants. Model C projects 2,593 (7.3 per 10,000). However, we consider Model B or Model D more likely for former East bloc countries. For Bosnia and Herzegovina, numbers of deceased people with DS in the national statistics are so low that no comparison with the model can be made.

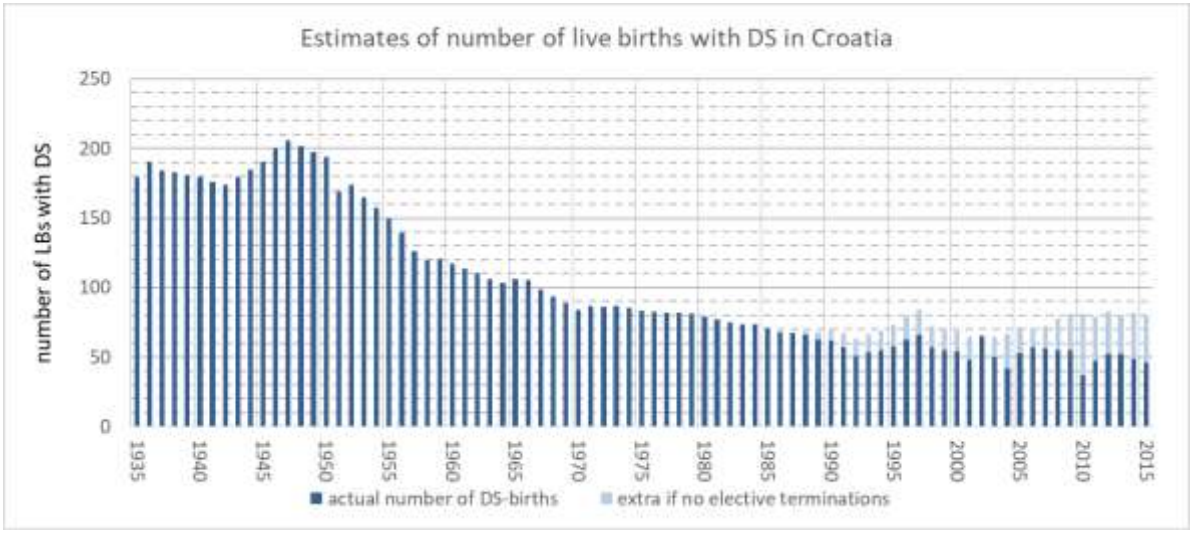


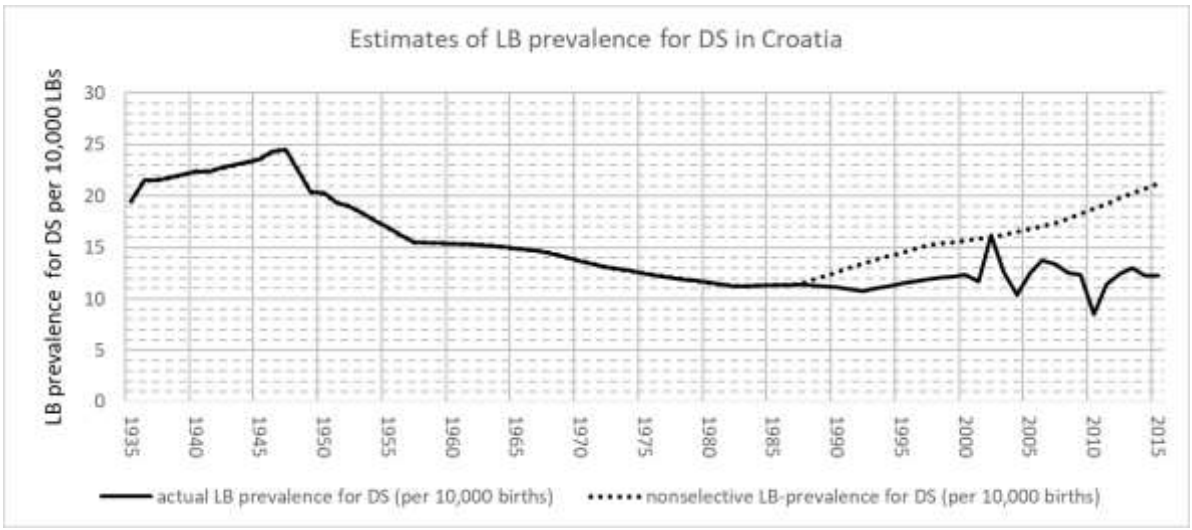


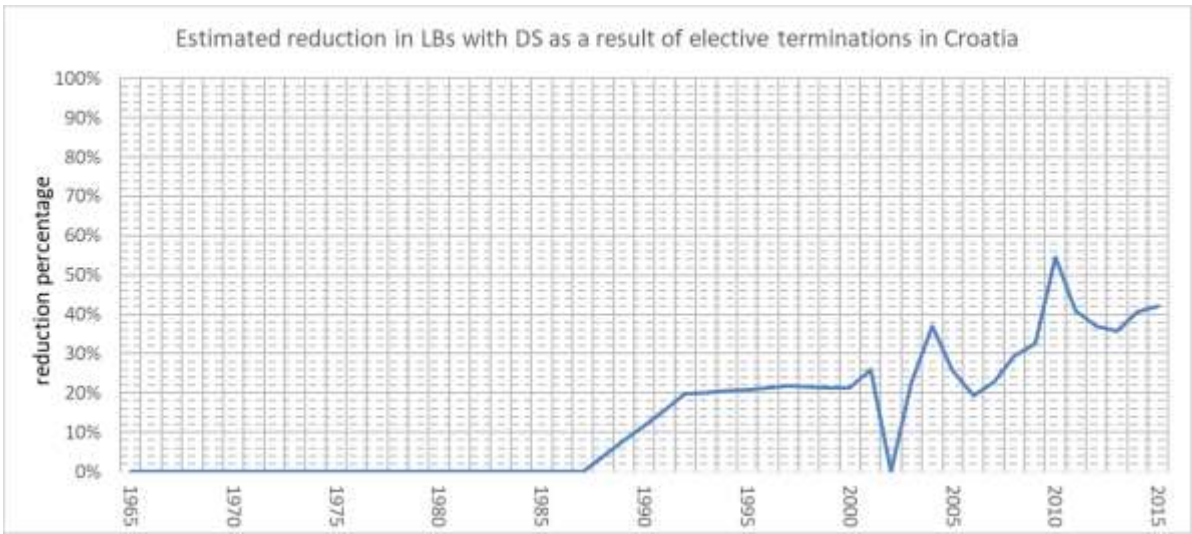

Estimated people with DS in Bosnia and Herzegovina, 1950-2015
2500
2000
1500
1000
500
0
7
6
5
4
3
2
1
0
276 272 284 308 336 408 479 553 676 899 1123 1298 1421 1505
297 312 360 474 597 737 865 1023 1258 1512 1744 1907 2009 2063
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Bosnia and Herzegovina by age group, as of 2015
model B
model D
300
250
200
150
100
50
0
12
11
10
9
8
7
6
5
4
3
2
1
0
126 151 196 244 229 172 121 106 79 49 22 8 2 1 0 0 0
126 152 199 257 247 210 173 119 74 32 7 0 0 0 0
269
197
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

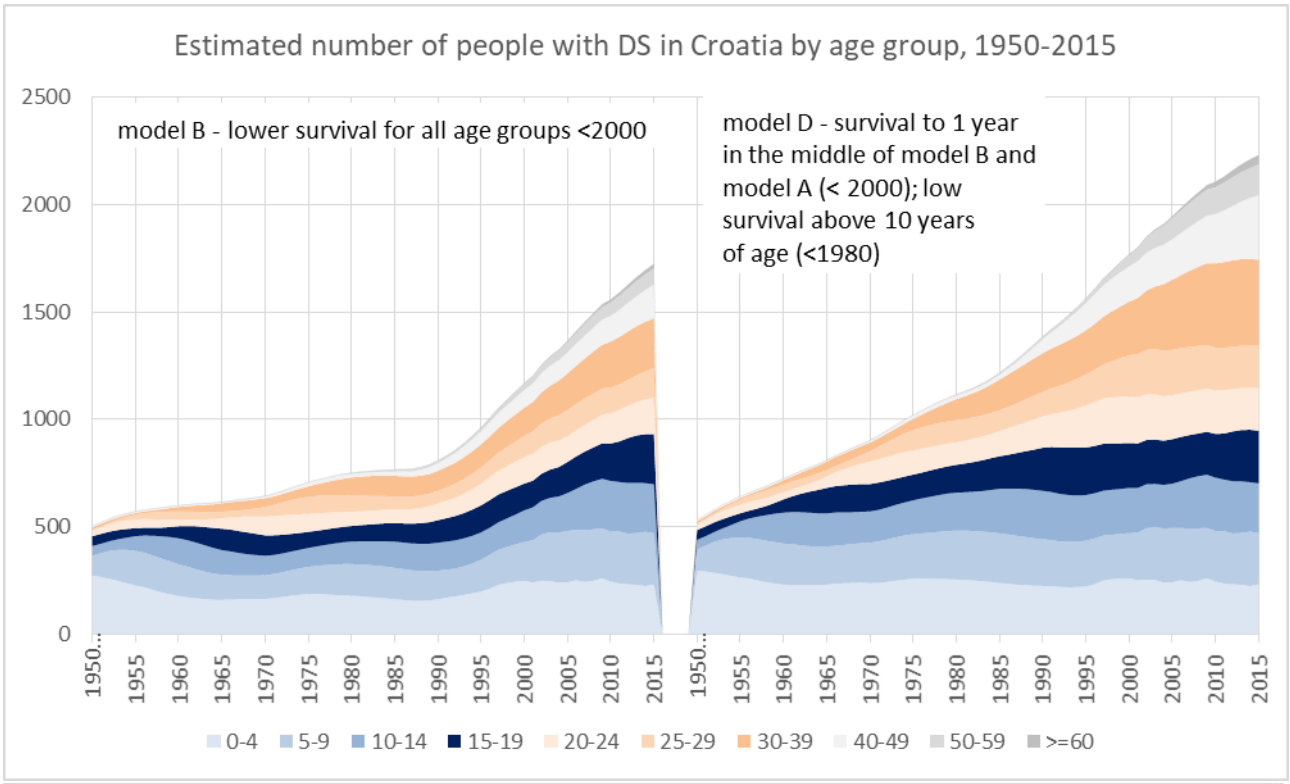
Croatia

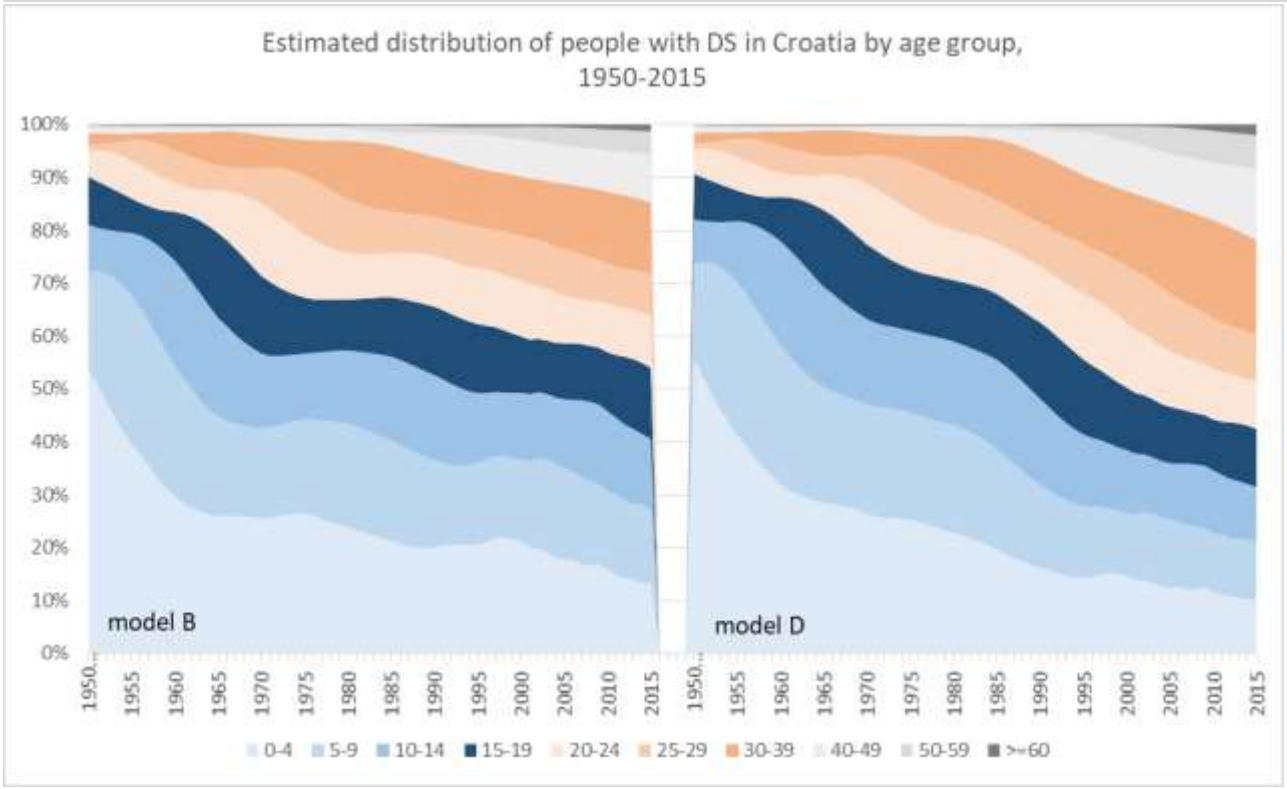

Estimates of number of live births with DS in Croatia
number of LBs with DS
250
200
150
100
50
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

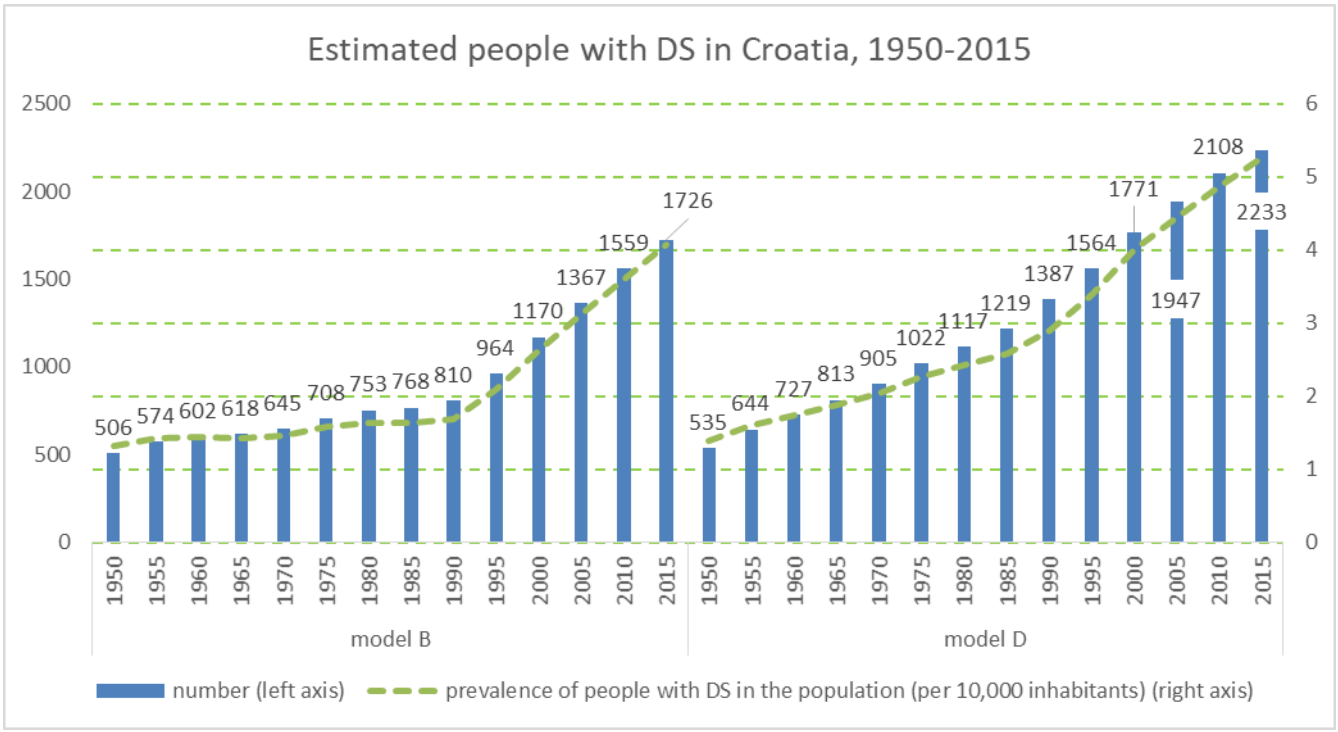

Estimates of LB prevalence for DS in Croatia
LB prevalence for DS per 10,000 LBs
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)

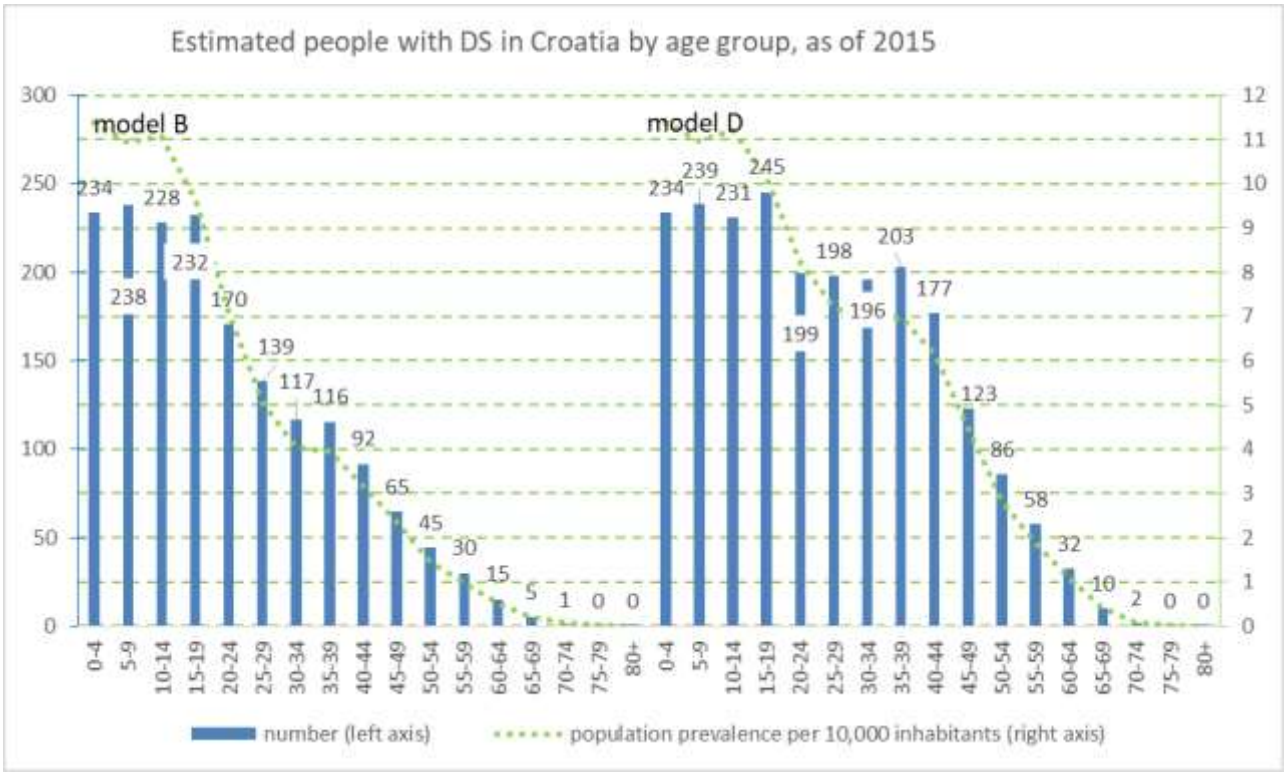

Estimated reduction in LBs with DS as a result of elective terminations in Croatia
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

Model A projects 2,906 people with DS alive in 2015, which corresponds to a population prevalence of 6.9 people with DS per 10,000 inhabitants. Model C projects 2,680 (6.3 per 10,000). However, we consider Model B or Model D more likely. Model B fits the data on number of people alive in Croatia, as of 2015, as reported by the Institute of Public Health (corrected for under-ascertainment) (see S5A). However, it is possible that under-ascertainment in the older age groups is larger than in younger people with DS. Model D seems to have the best fit as regards age distribution of deaths with DS from national statistics (see S5C) for 2005–2015.

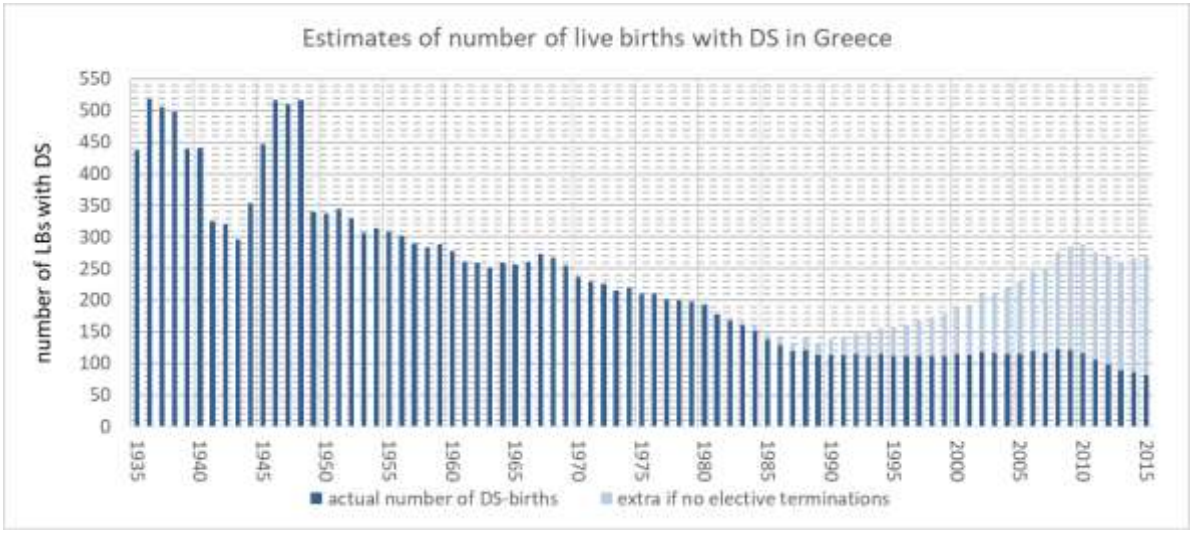


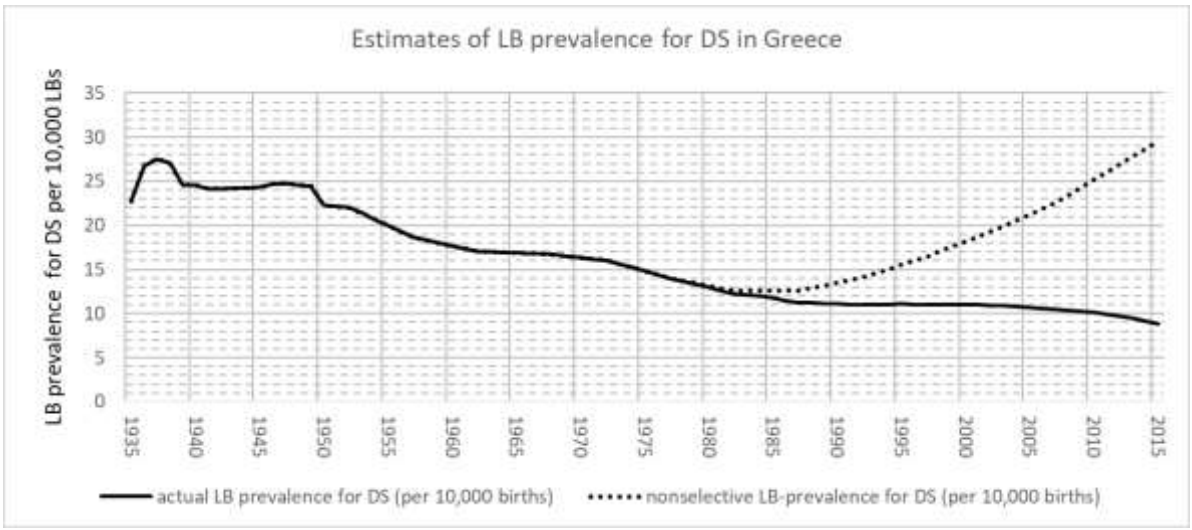


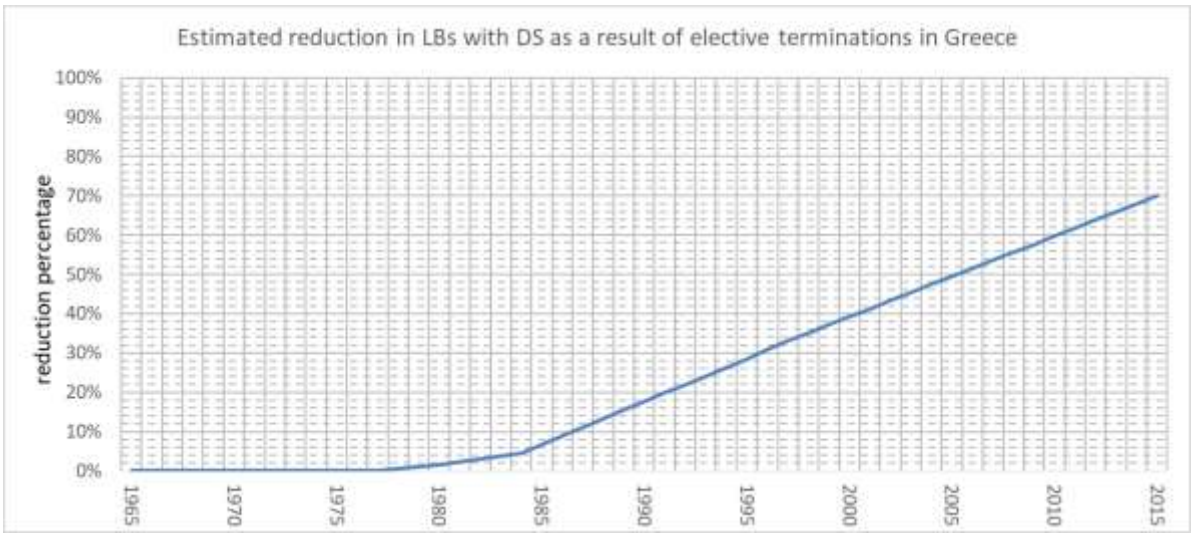

Estimated people with DS in Croatia, 1950-2015
2500
2000
1500
1000
500
0
6
5
4
3
2
1
0
506 574 602 618 645 708 753 768 810 964 1170 1367 1559 1726
535 644 727 813 905 1022 1117 1219 1387 1564 1771 1947 2108 2233
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

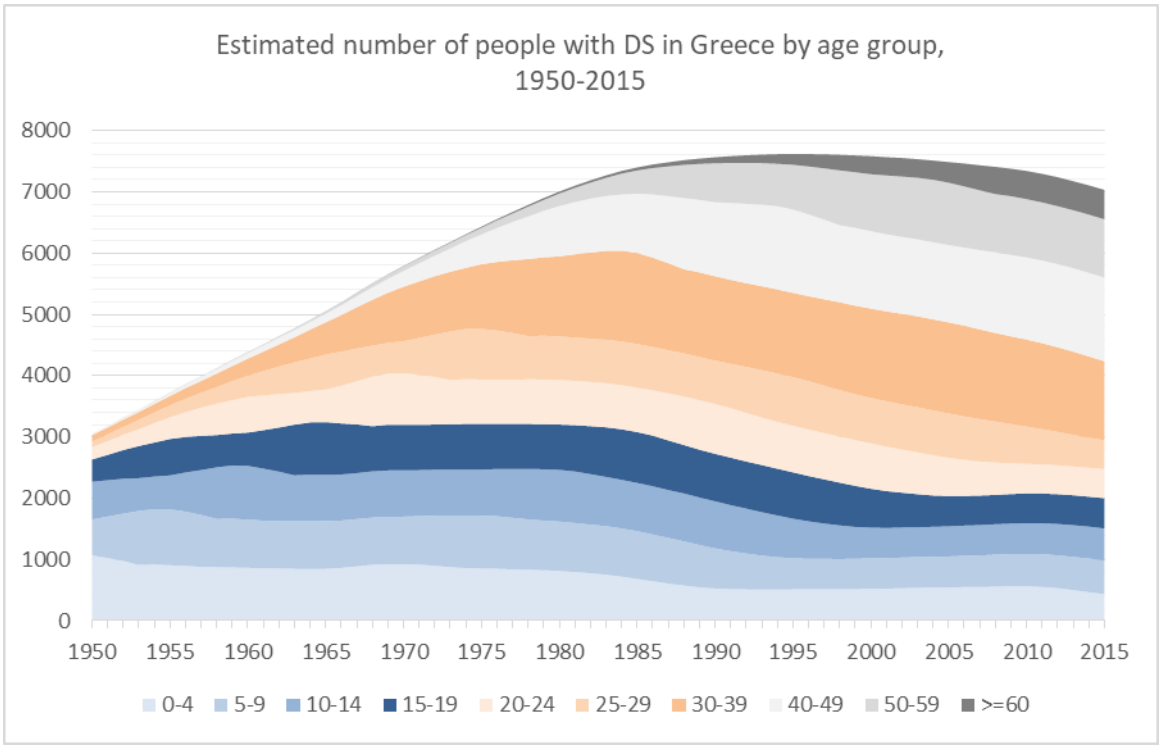

Estimated people with DS in Croatia by age group, as of 2015
model B
model D
300
250
200
150
100
50
0
12
11
10
9
8
7
6
5
4
3
2
1
0
234 238 228 232 170 139 117 116 92 65 45 30 15 5 1 0 0
234 239 231 245 199 198 196 203 177 123 86 58 32 10 2 0 0
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

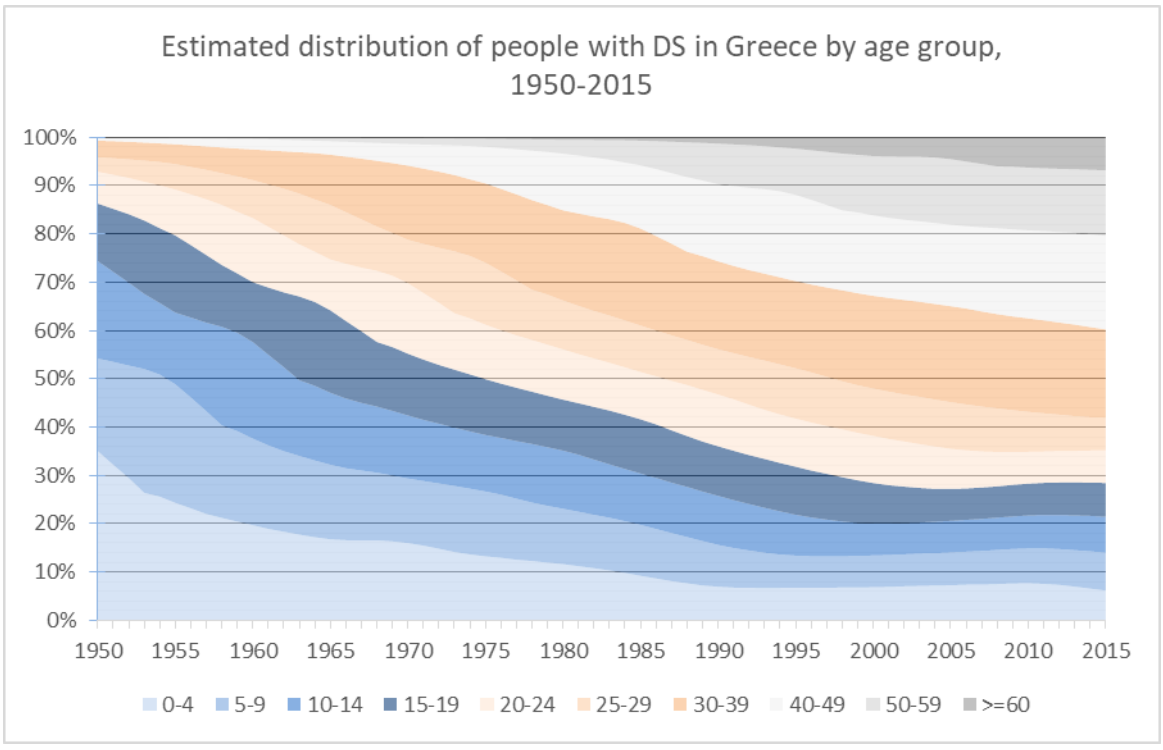
Greece

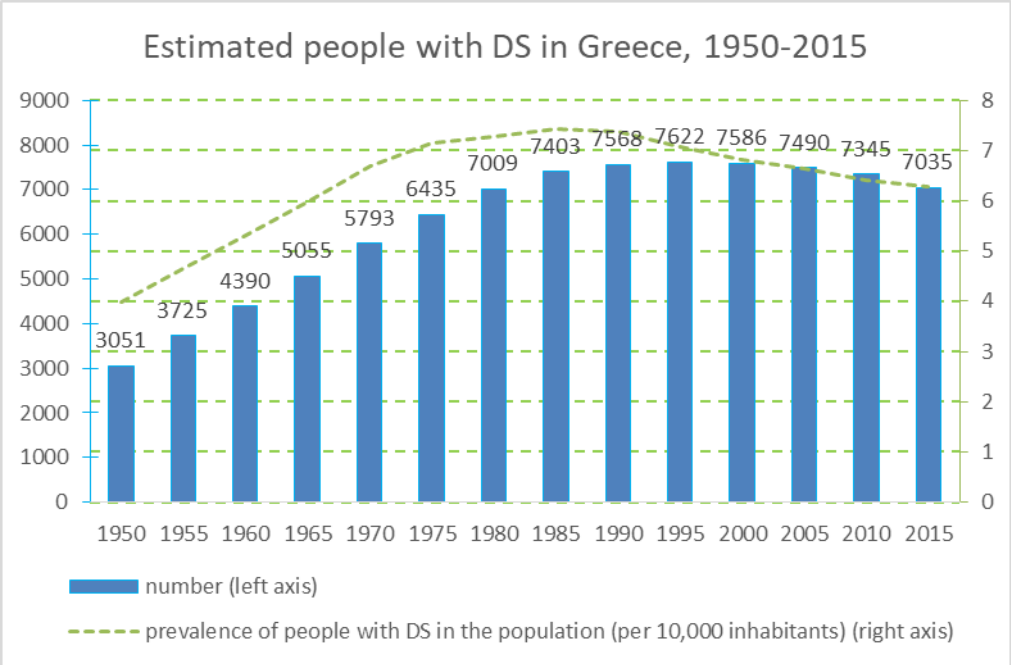

Estimates of number of live births with DS in Greece
number of LBs with DS
550
500
450
400
350
300
250
200
150
100
50
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

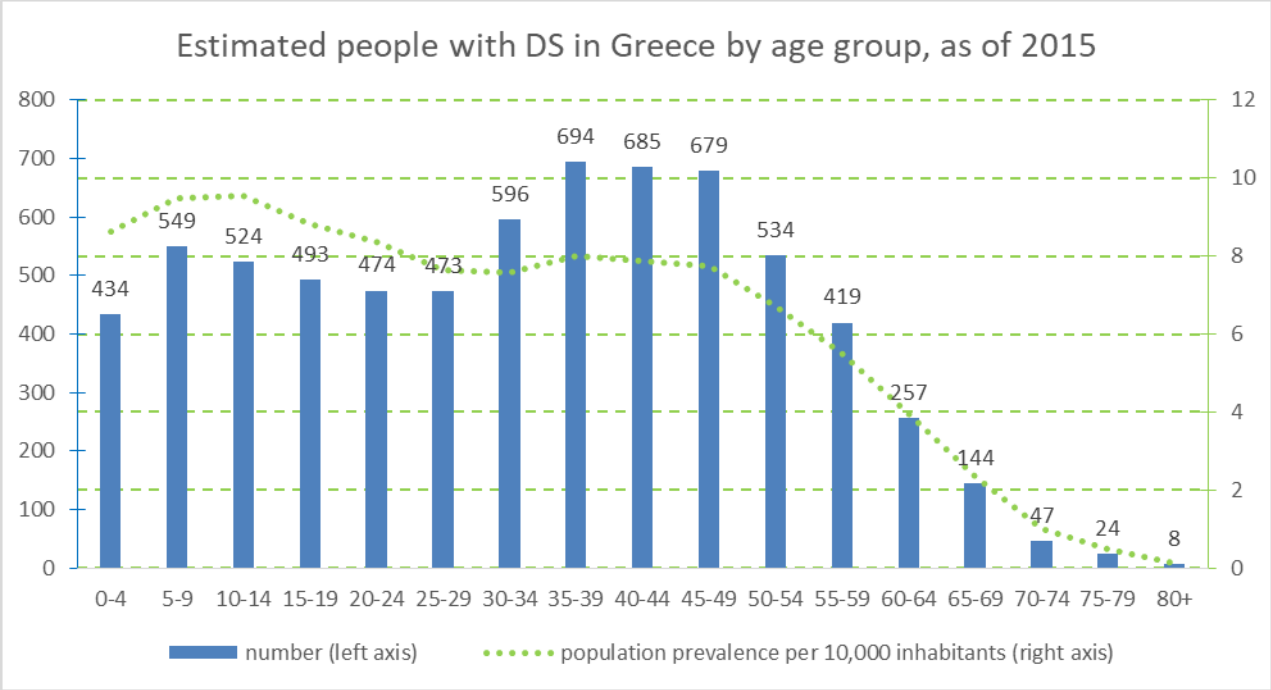

Estimates of LB prevalence for DS in Greece
LB prevalence for DS per 10,000 LBs
35
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Greece
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

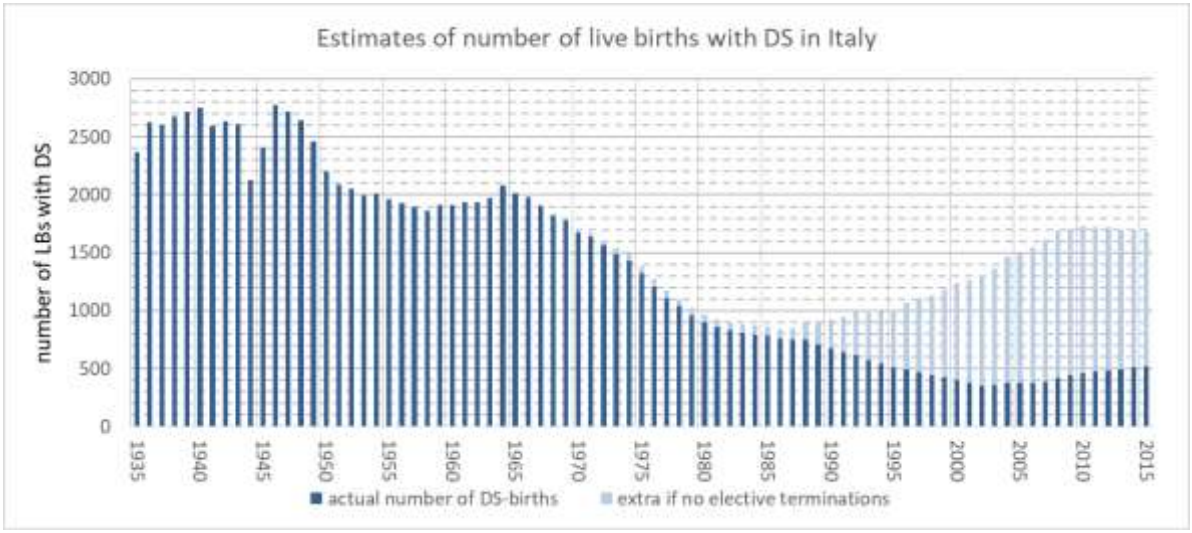

Estimated number of people with DS in Greece by age group, 1950-2015
8000
7000
6000
5000
4000
3000
2000
1000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

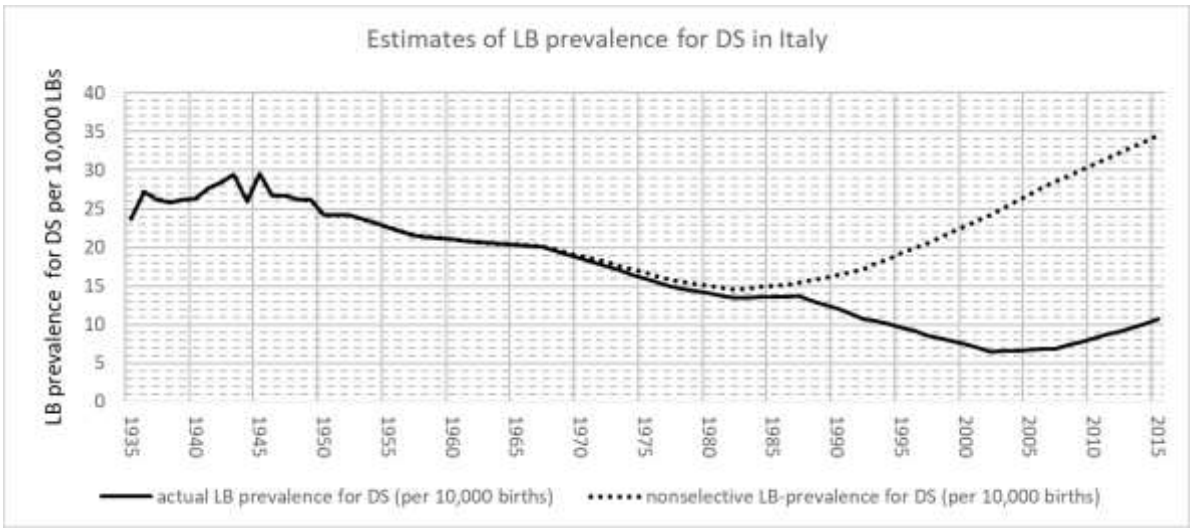

Estimated distribution of people with DS in Greece by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

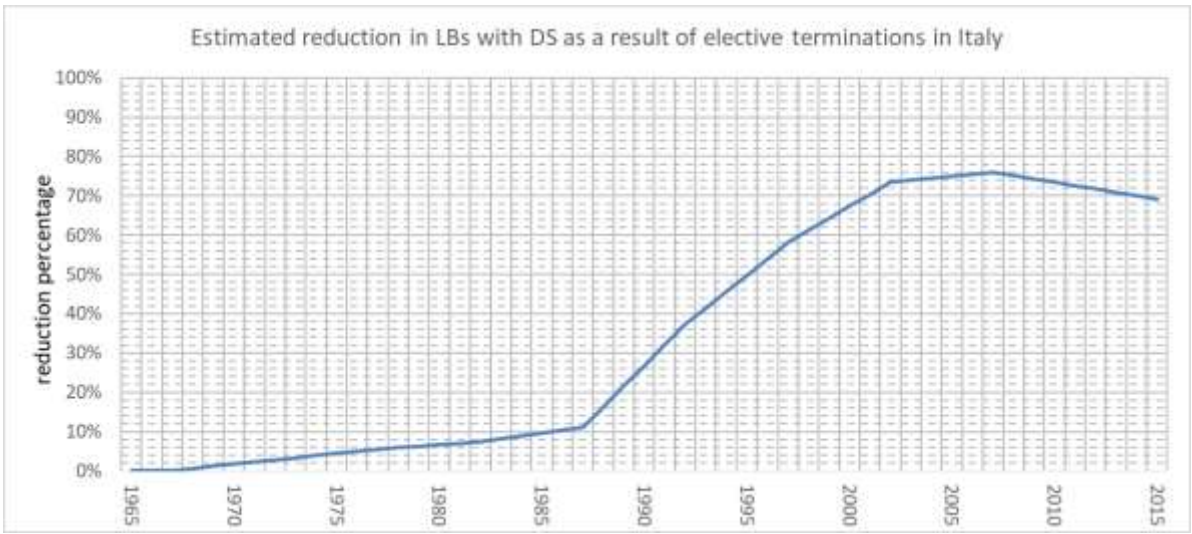

Estimated people with DS in Greece, 1950-2015
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
8
7
6
5
4
3
2
1
0
3051
3725
4390
5055
5793
6435
7009
7403
7568
7622
7586
7490
7345
7035
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

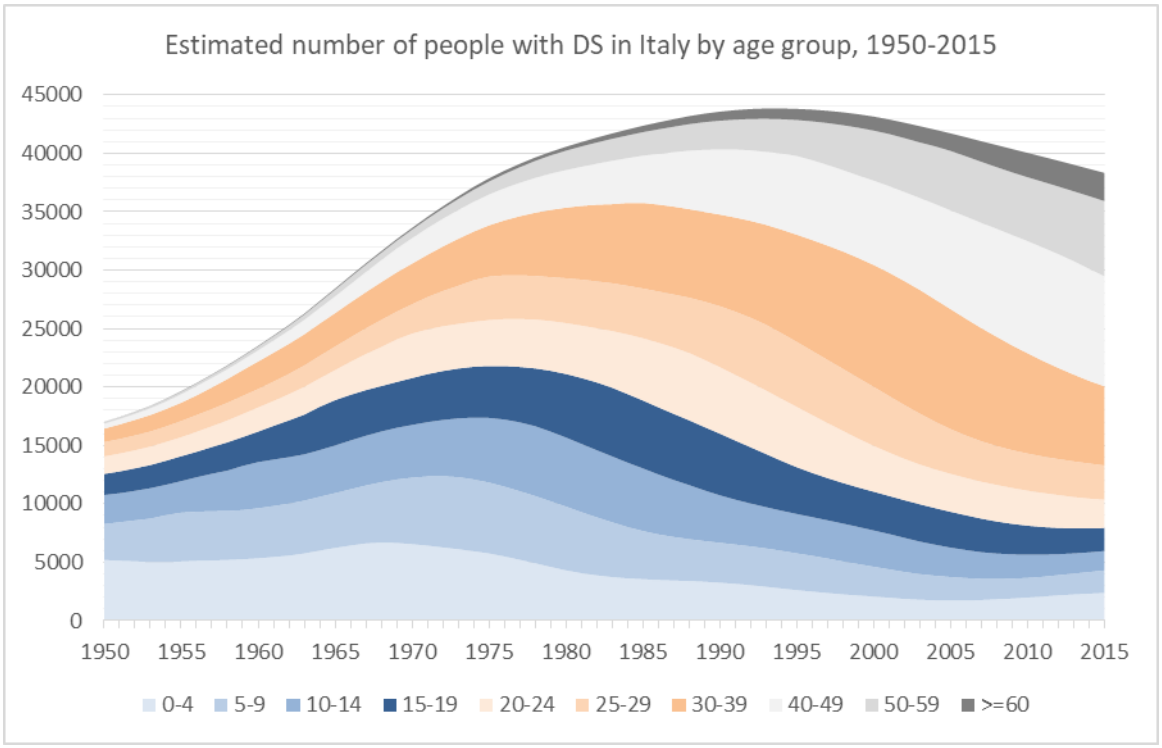

Estimated people with DS in Greece by age group, as of 2015
800
700
600
500
400
300
200
100
0
12
10
8
6
4
2
0
434
549
524
493
474
473
596
694
685
679
534
419
257
144
47
24
8
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

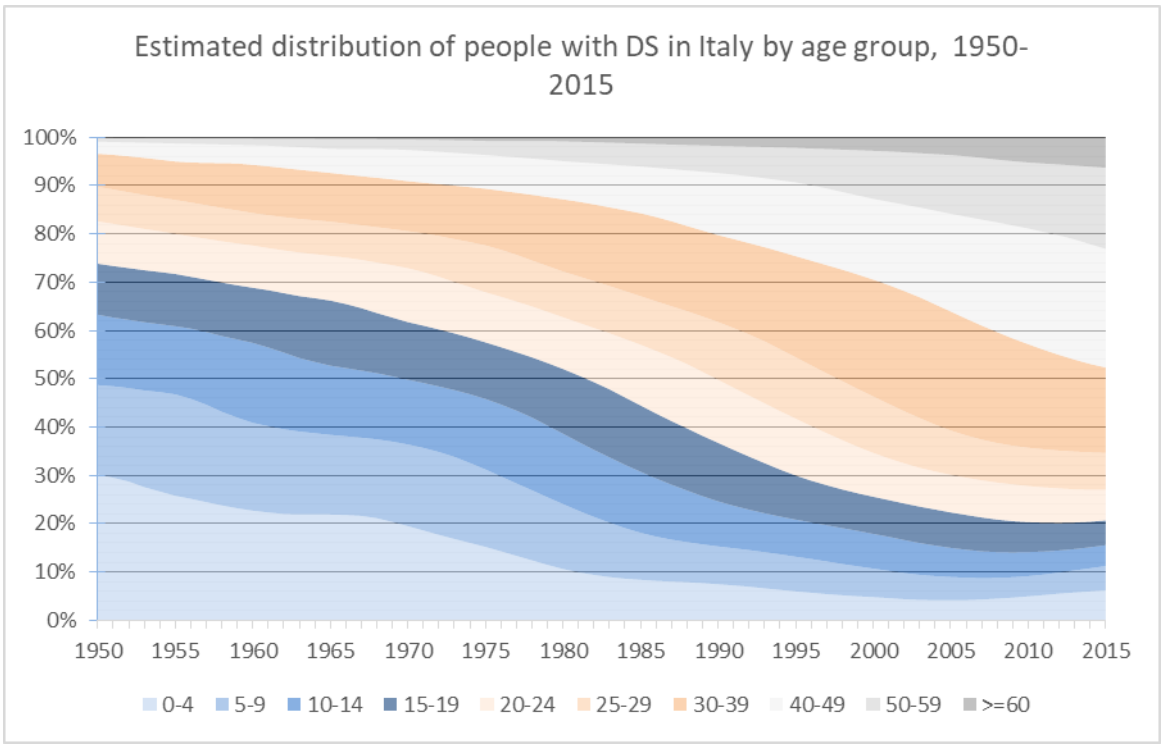
Italy

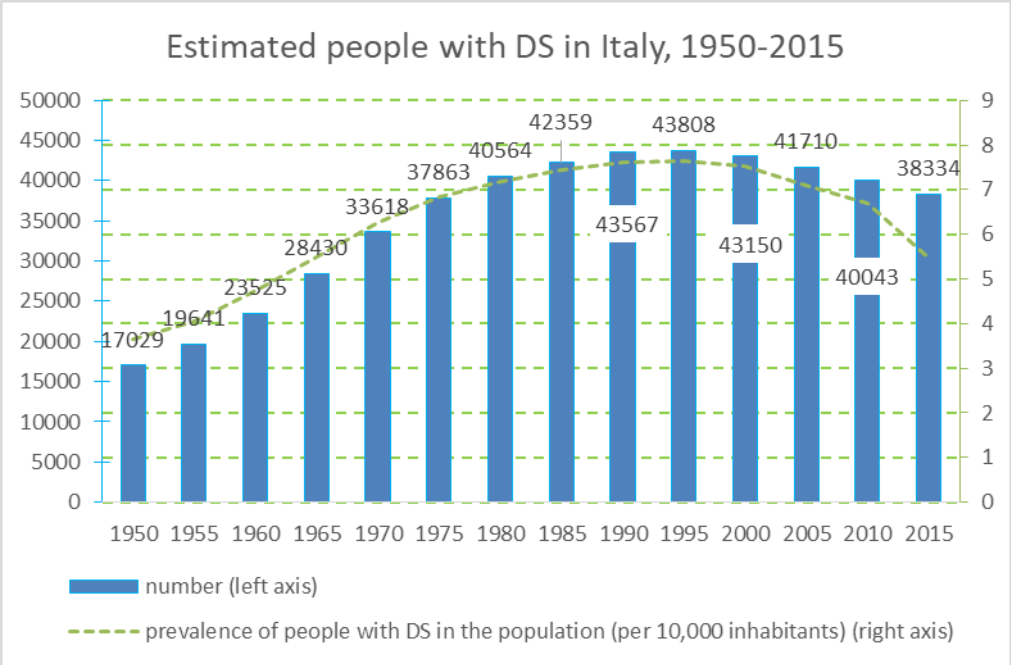

Estimates of number of live births with DS in Italy
number of LBs with DS
3000
2500
2000
1500
1000
500
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

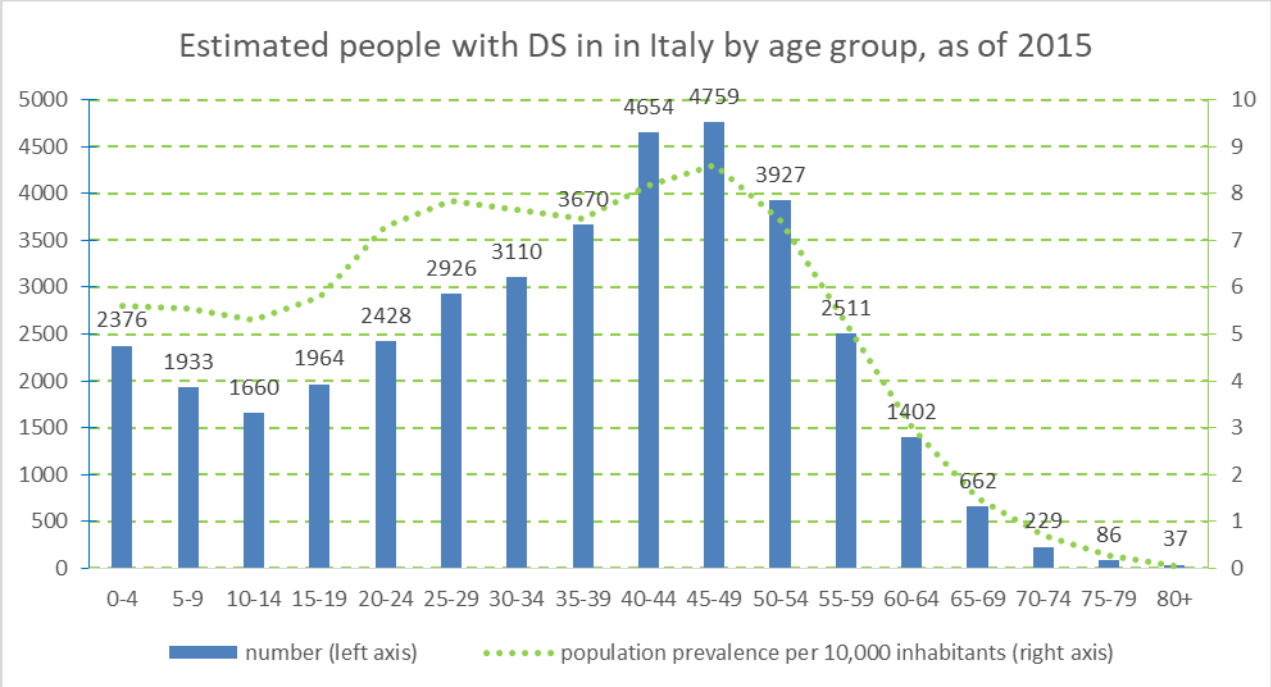

Estimates of LB prevalence for DS in Italy
LB prevalence for DS per 10,000 LBs
40
35
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Italy
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

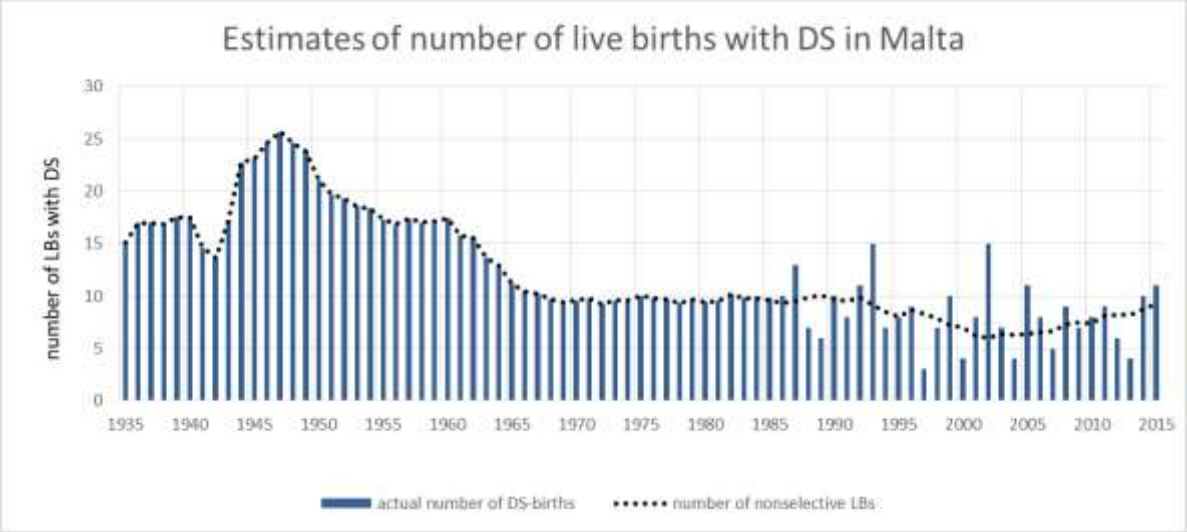

Estimated number of people with DS in Italy by age group, 1950-2015
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60


Estimated distribution of people with DS in Italy by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

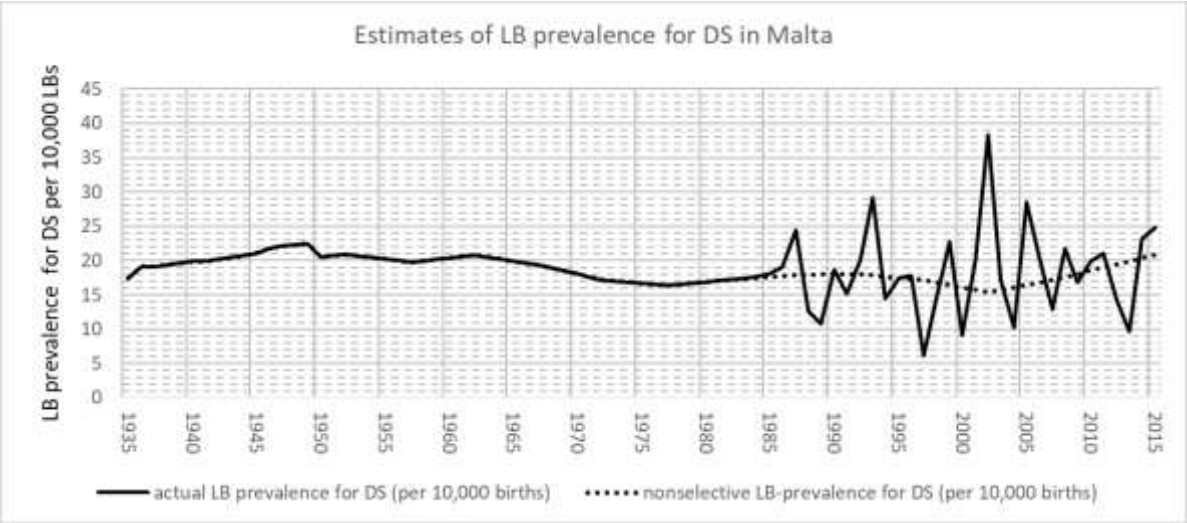

Estimated people with DS in Italy, 1950-2015
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
9
8
7
6
5
4
3
2
1
0
17029
19641
23525
28430
33618
37863
40564
42359
43567
43808
43150
41710
40043
38334
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in in Italy by age group, as of 2015
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10
9
8
7
6
5
4
3
2
1
0
2376
1933
1660
1964
2428
2926
3110
3670
4654
4759
3927
2511
1402
662
229
86
37
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Malta

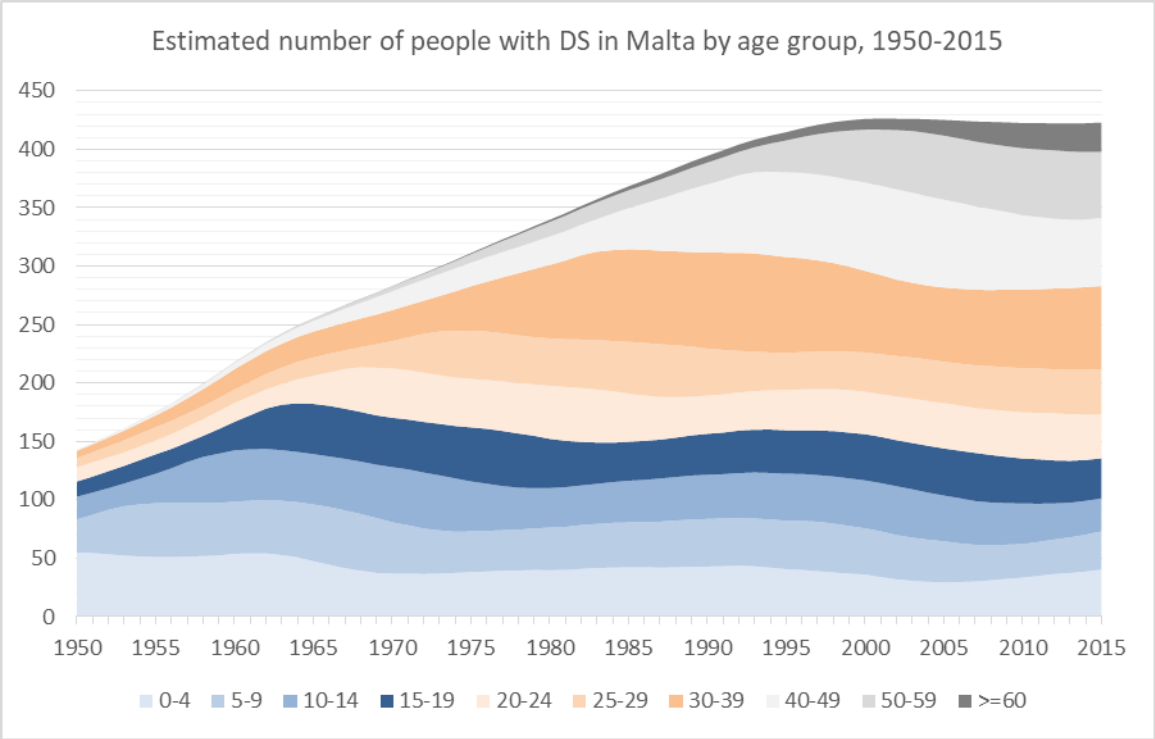


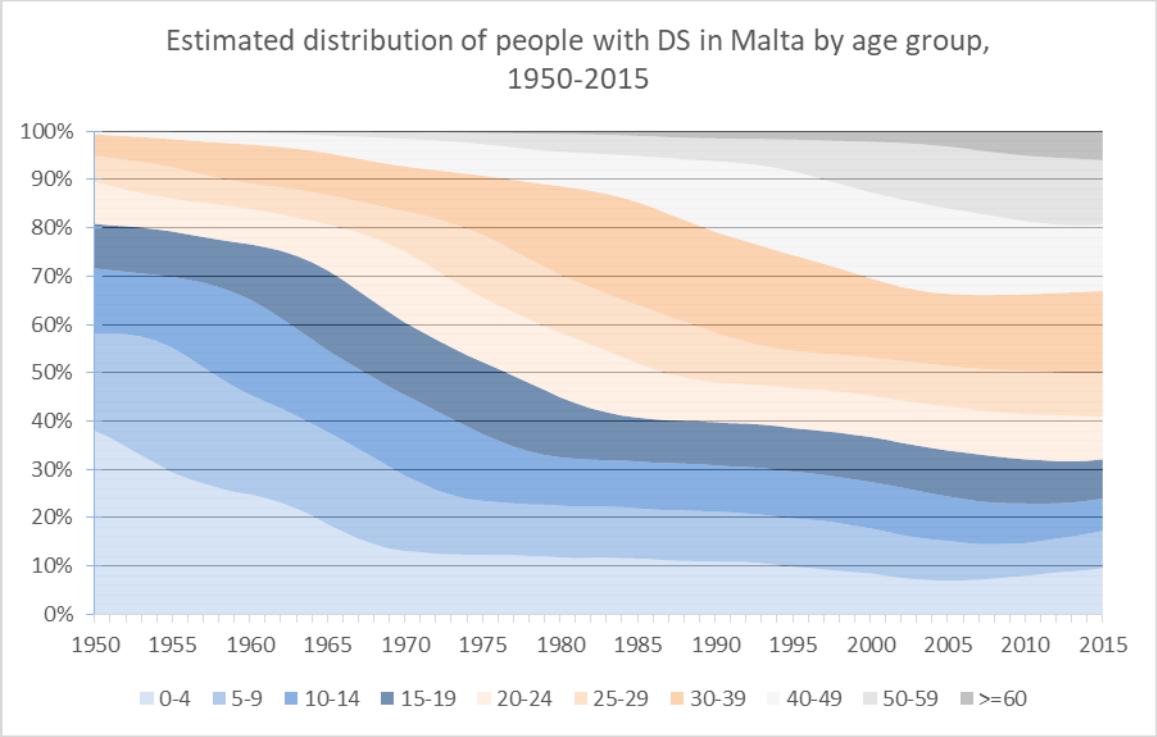
As termination is illegal is Malta, reduction percentage is presumed to be zero. The blue bars, from 1986 onwards, are the actual numerical counts from EUROCAT. The black line represents our modeled nonselective numbers. The total numbers, if grouped by 10-year period, are almost the same. In the period 1986–1995, EUROCAT counted 95 LBs of children with DS; our model predicts 95. For 1996–2005, these numbers are 78 and 72 (8% difference), respectively. For 2006–2015, they are 77and 77.

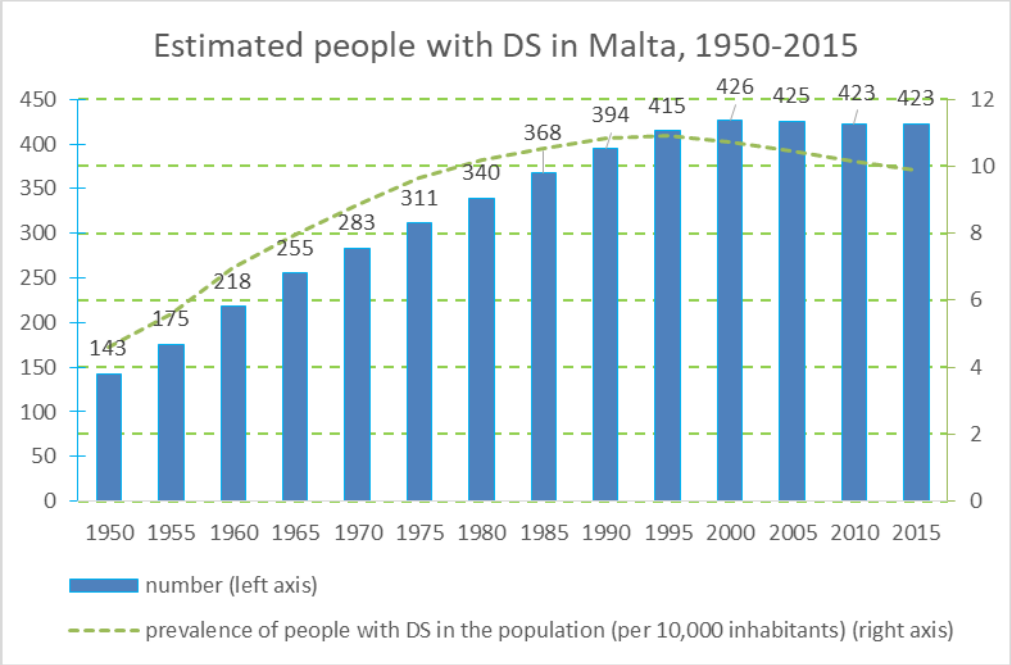


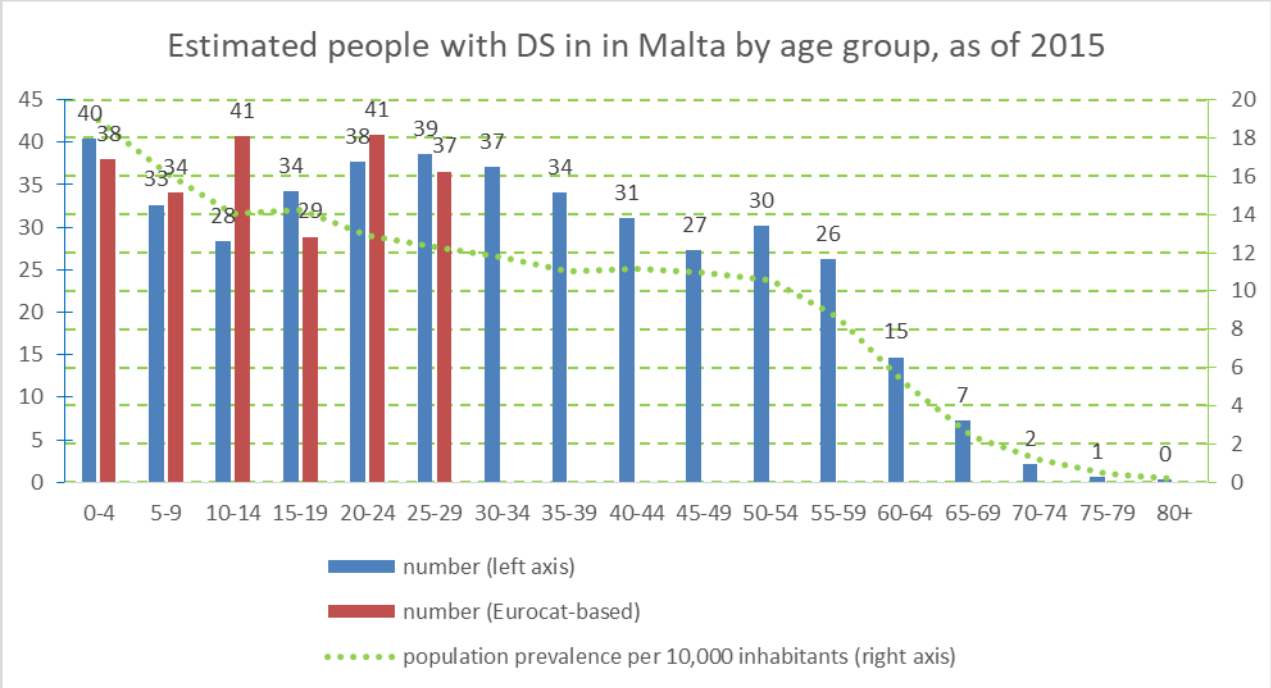
As the number of births is small in Malta, there is huge random fluctuation by year in the actual number of LBs of DS.

The graph about reduction percentage is left out. Termination is illegal in Malta. Therefore, reduction percentage will be around zero, as is confirmed by the fact that the total numbers of nonselective births (as modeled) and the actual live births (as counted by EUROCAT), if grouped by 10-year period, are almost the same.


Estimated number of people with DS in Malta by age group, 1950-2015
450
400
350
300
250
200
150
100
50
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

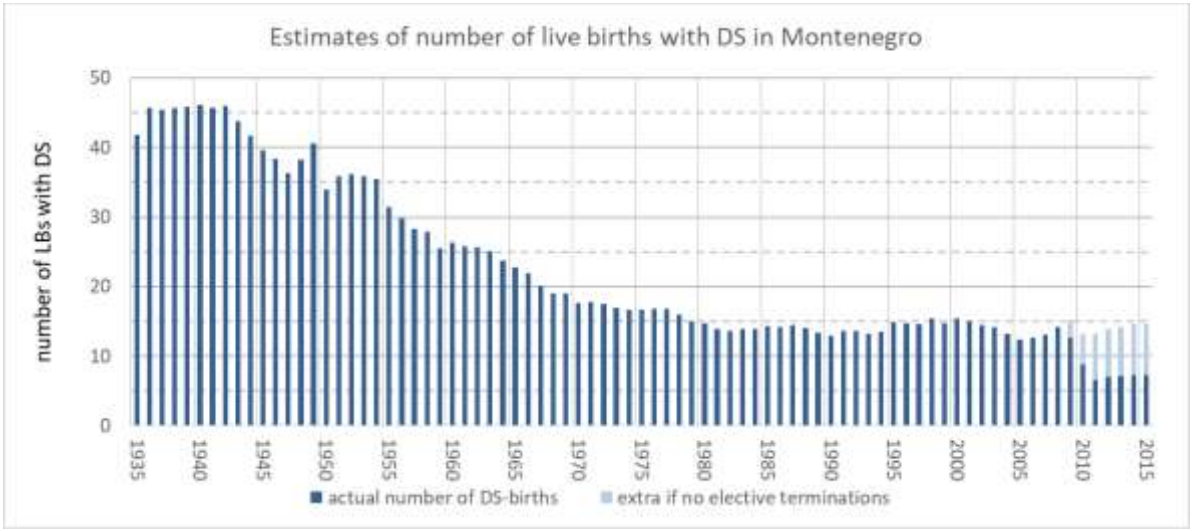

Estimated distribution of people with DS in Malta by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

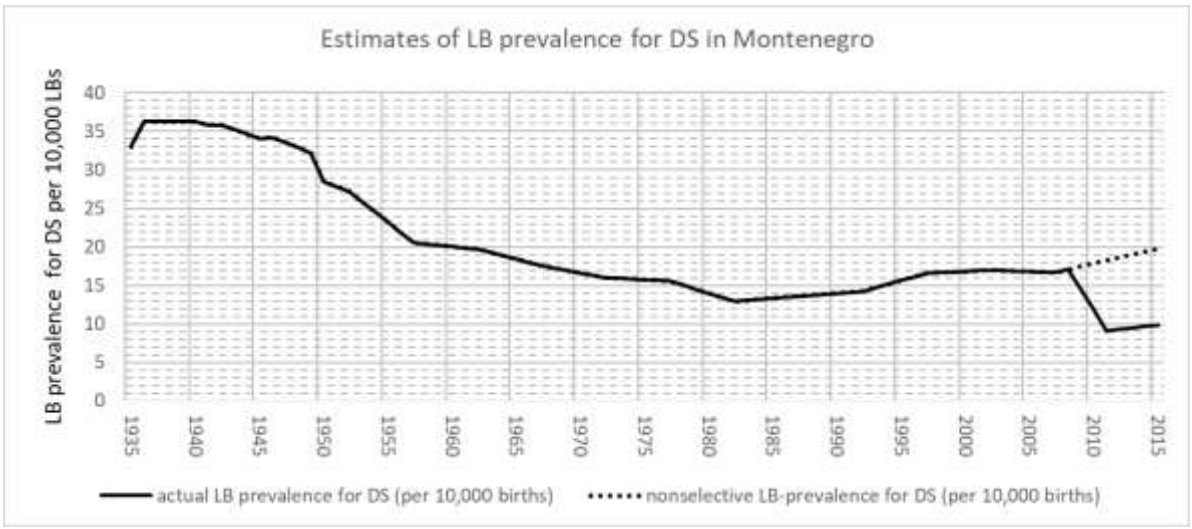


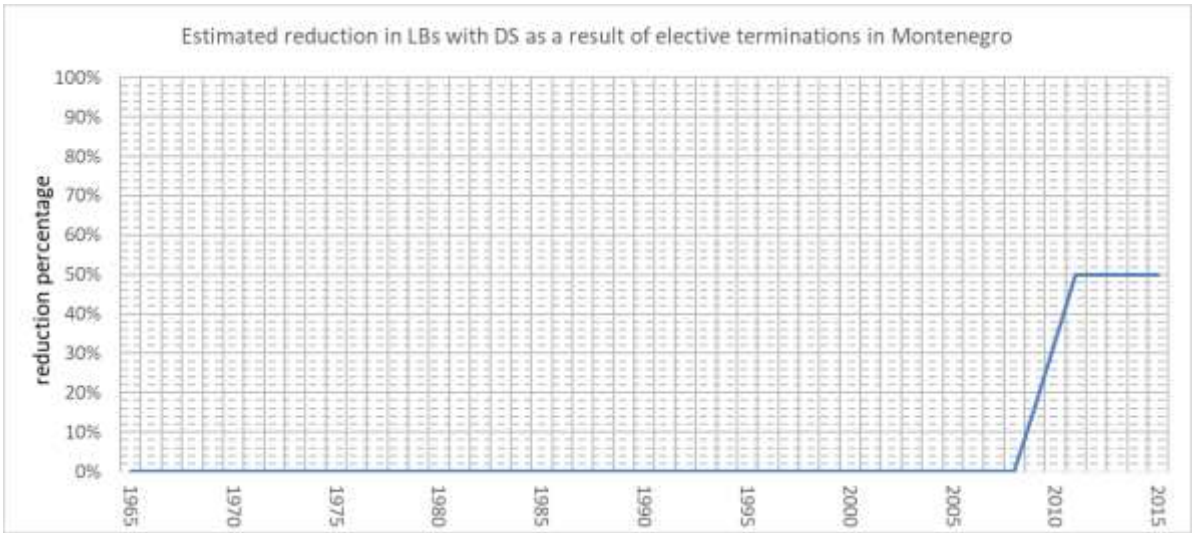


For comparison, we have added the estimated numbers by age group based on EUROCAT counts of LBs with DS for the age groups born after 1985. Total number of people with DS alive in 2015 would have been 430 based on EUROCAT counts of LBs, instead of 423 as modeled (difference less than 2%).

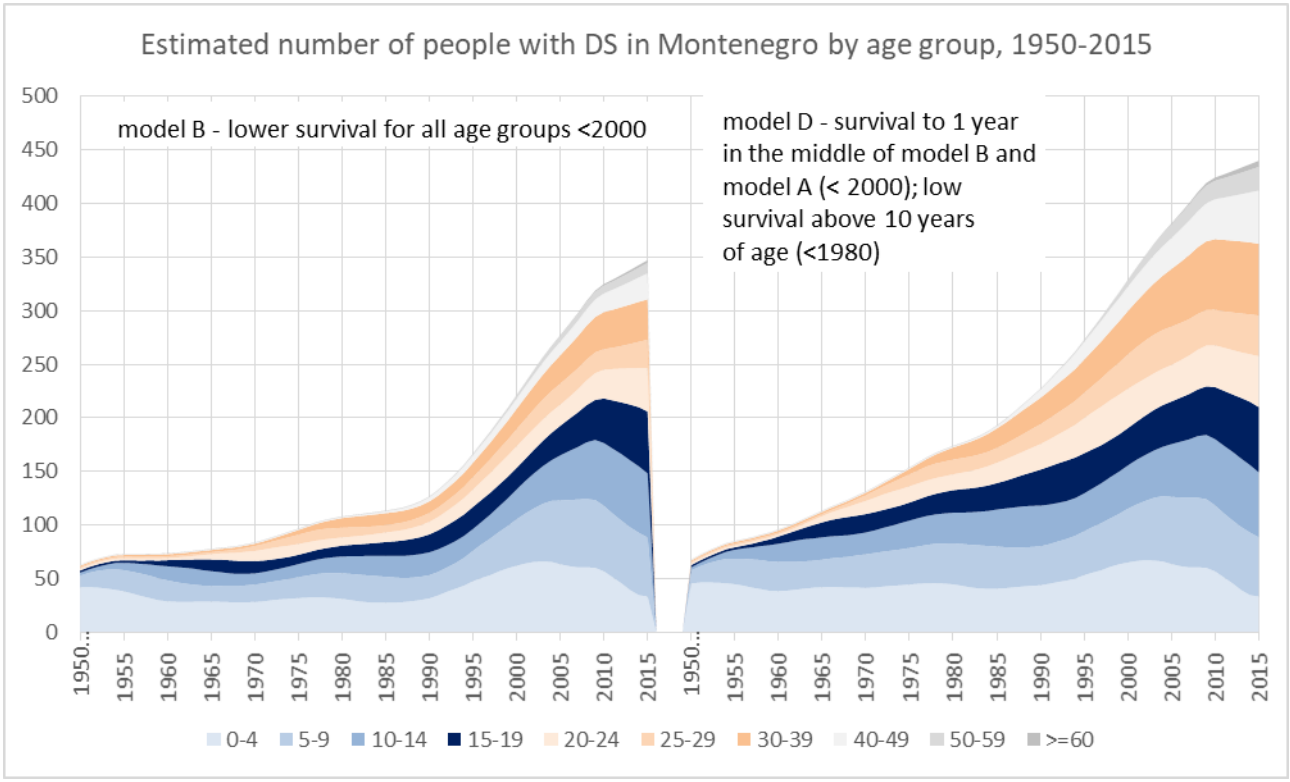
Montenegro

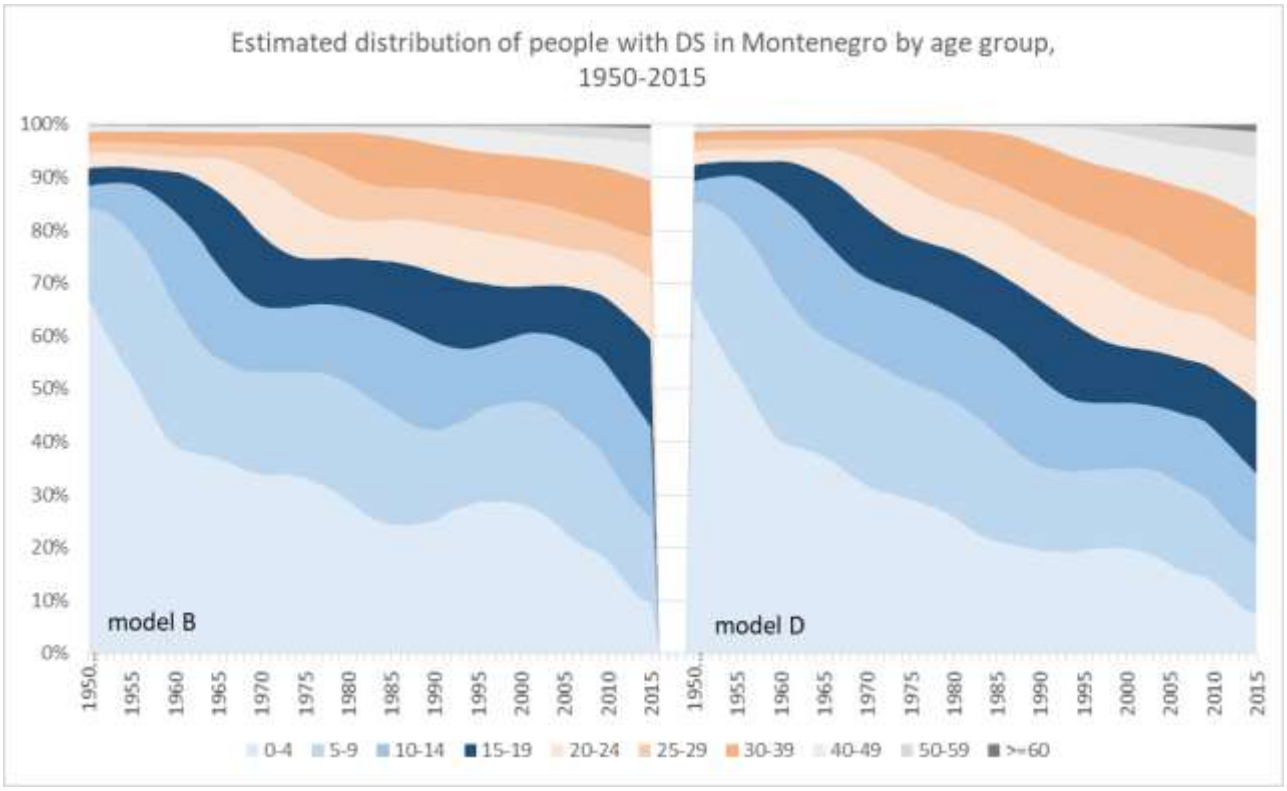

Estimates of number of live births with DS in Montenegro
number of LBs with DS
50
40
30
20
10
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

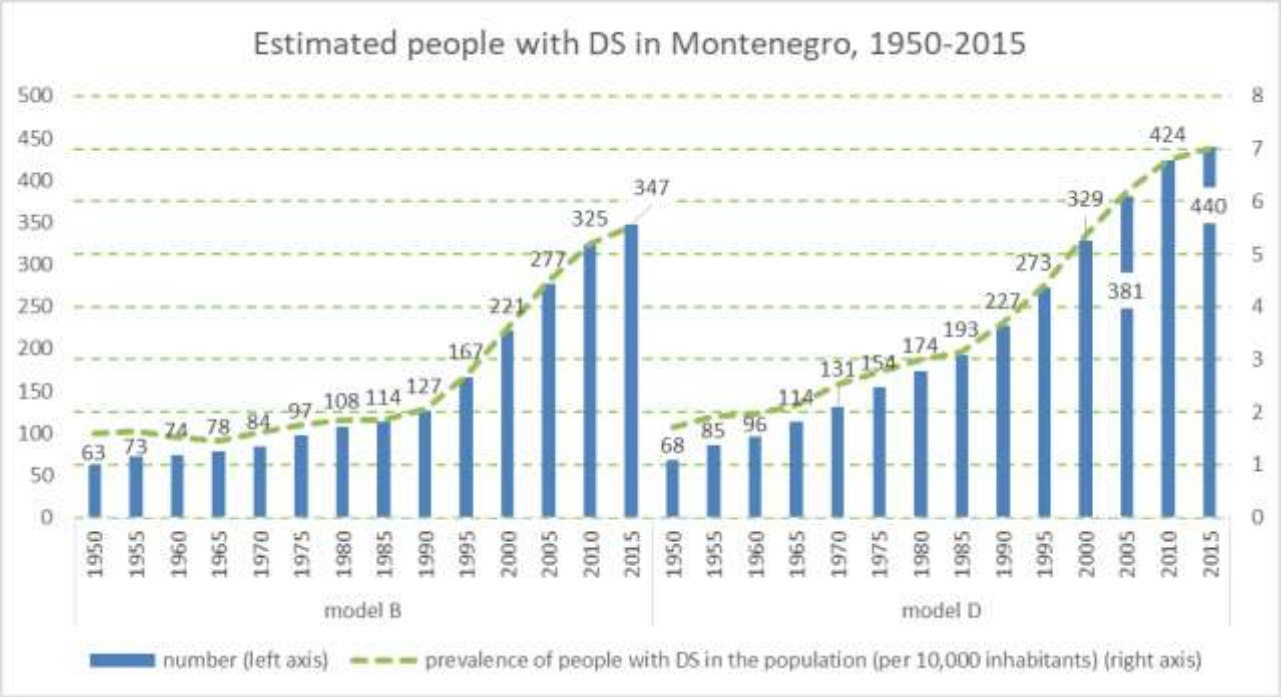

Estimates of LB prevalence for DS in Montenegro
LB prevalence for DS per 10,000 LBs
40
35
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)

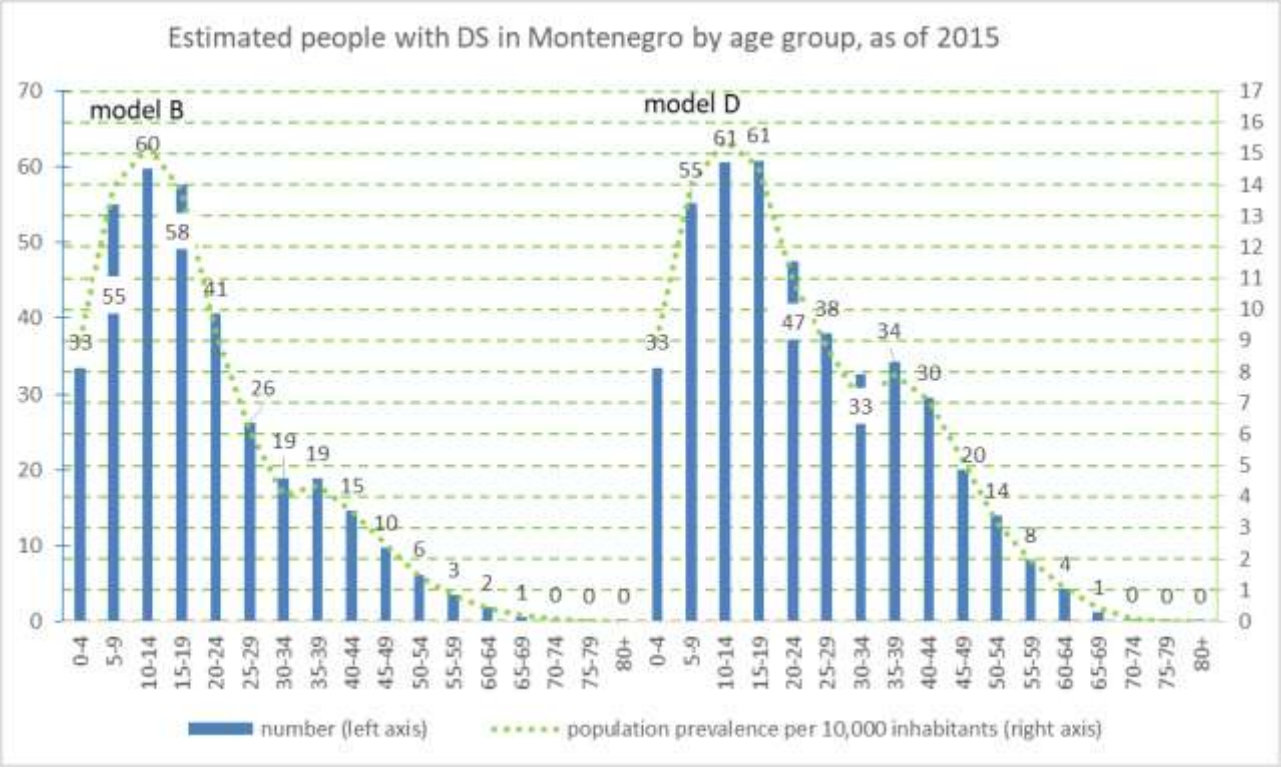

Estimated reduction in LBs with DS as a result of elective terminations in Montenegro
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

Model A projects 556 people with DS alive in 2015, which corresponds to a population prevalence of 8.9 people with DS per 10,000 inhabitants. Model C projects 524 (8.3 per 10,000). However, we consider Model B or Model D more likely for former-East bloc countries. For Montenegro, numbers of deceased people with DS in the national statistics are so low that no comparison with the model can be made.

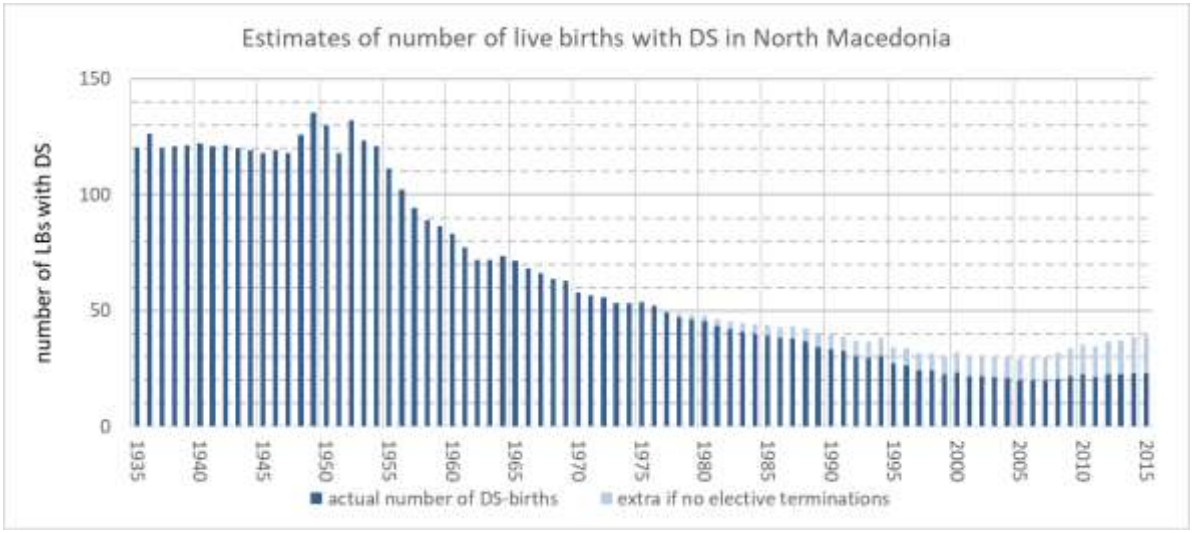


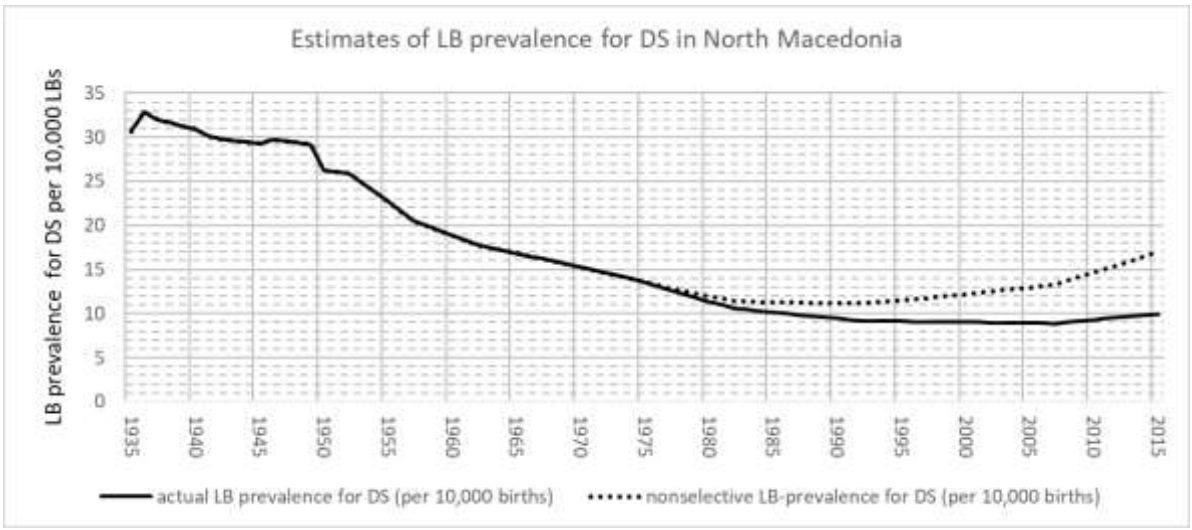


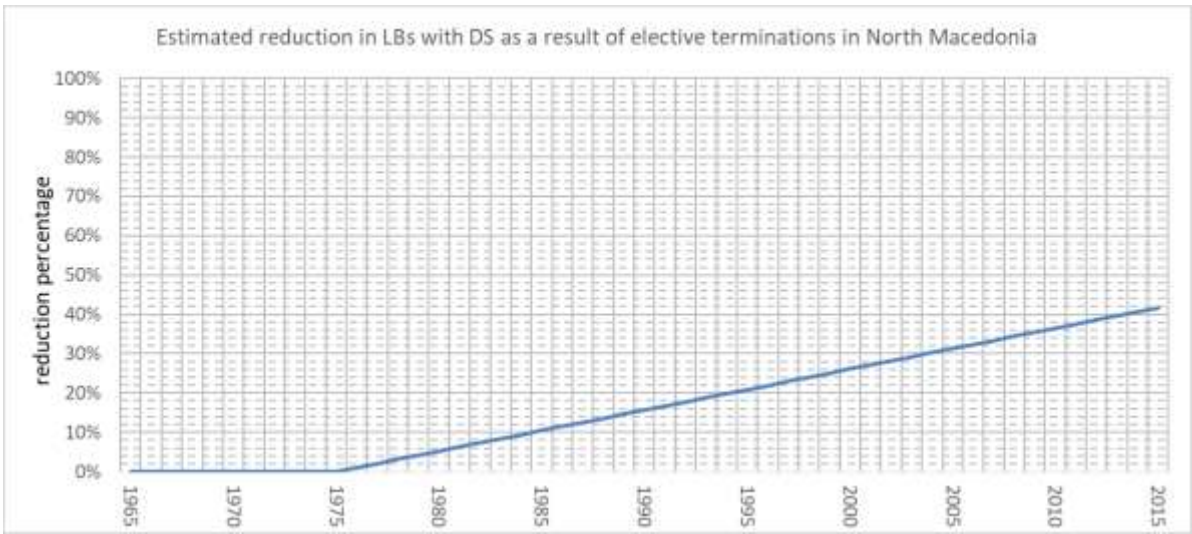

Estimated people with DS in Montenegro, 1950-2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Montenegro by age group, as of 2015
model B
model D
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

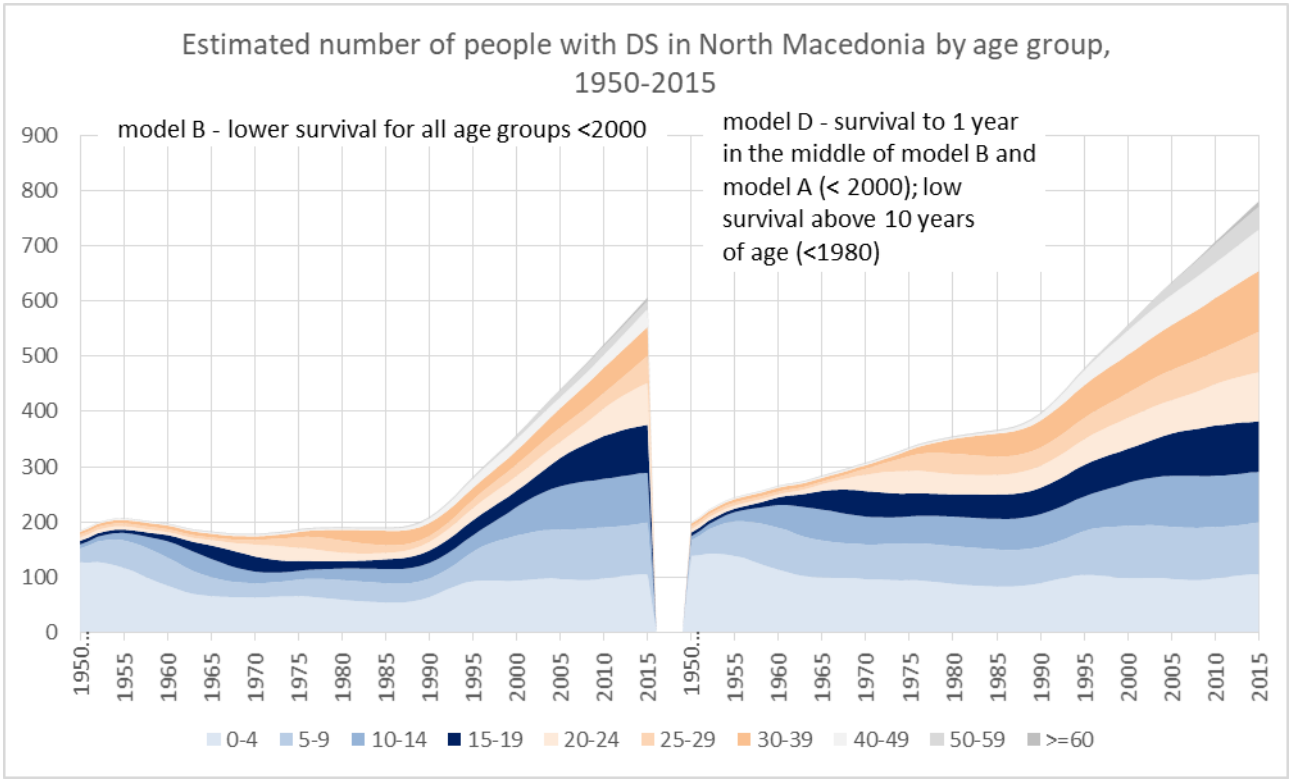
North Macedonia

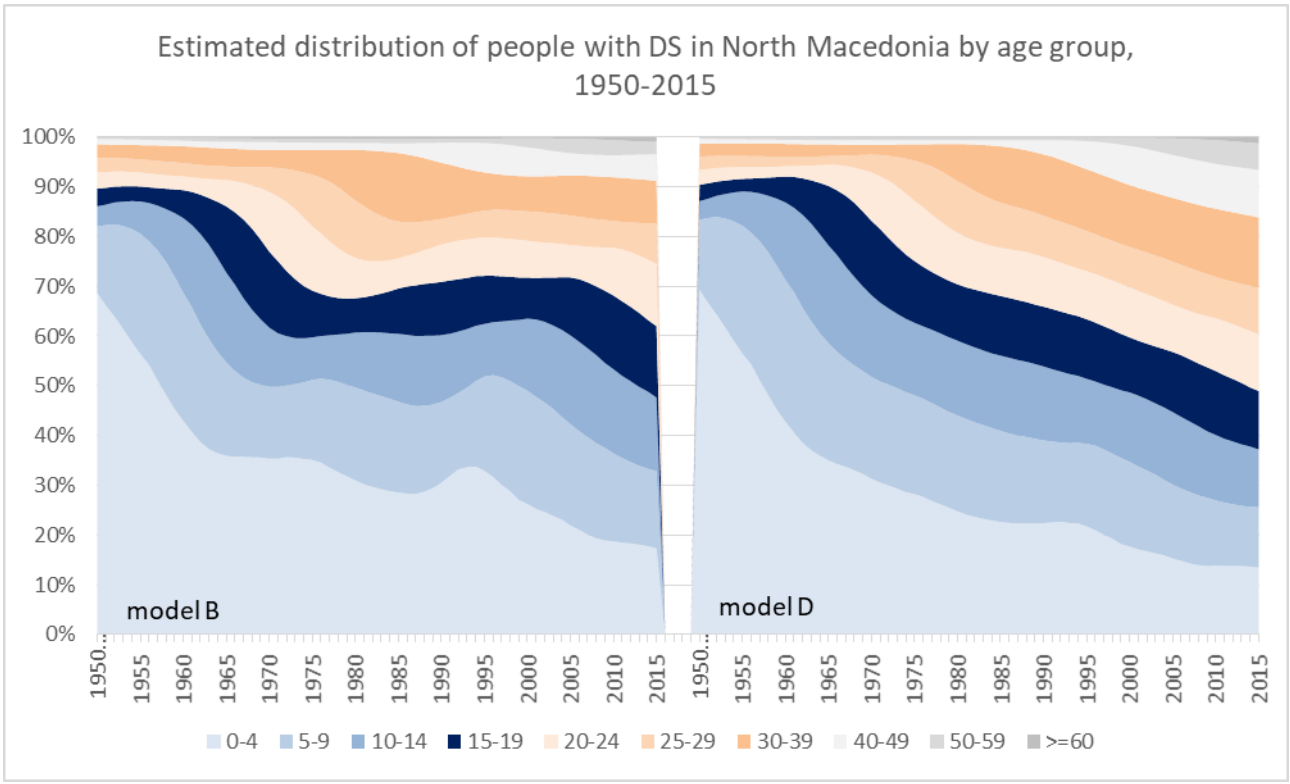


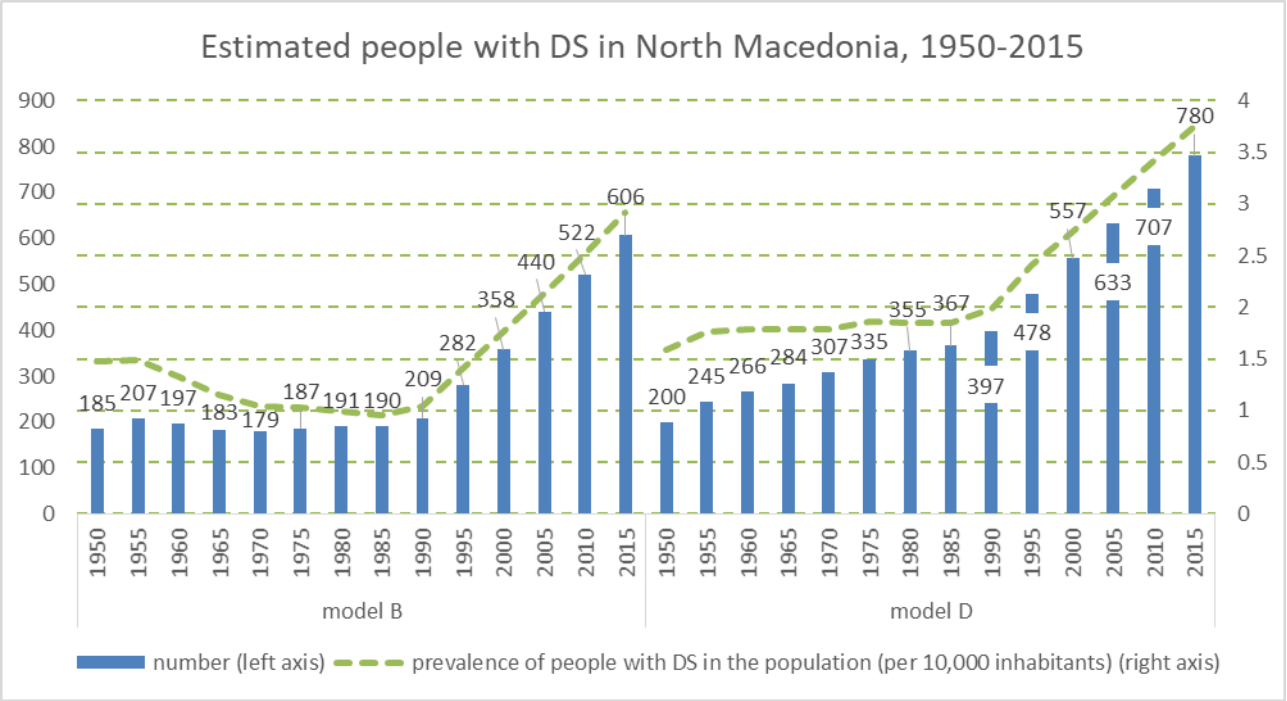


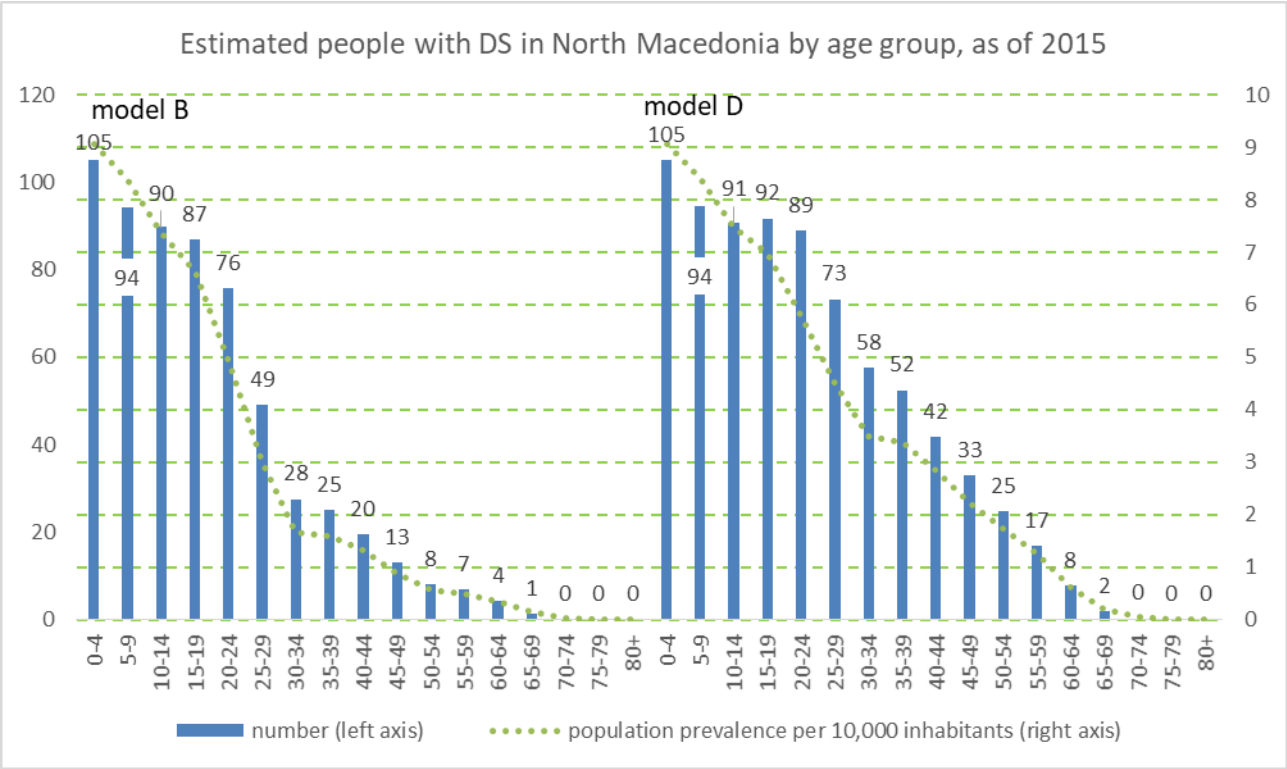


Both model A and Model C project 996 people with DS alive in 2015, which corresponds to a population prevalence of 4.8 people with DS per 10,000 inhabitants. However, both these models are unlikely, as their projections don't fit the data on age distribution of deaths with DS (see S5C). Model B and Model D are depicted in the graphs. For North Macedonia, Model B seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics (see S5C).

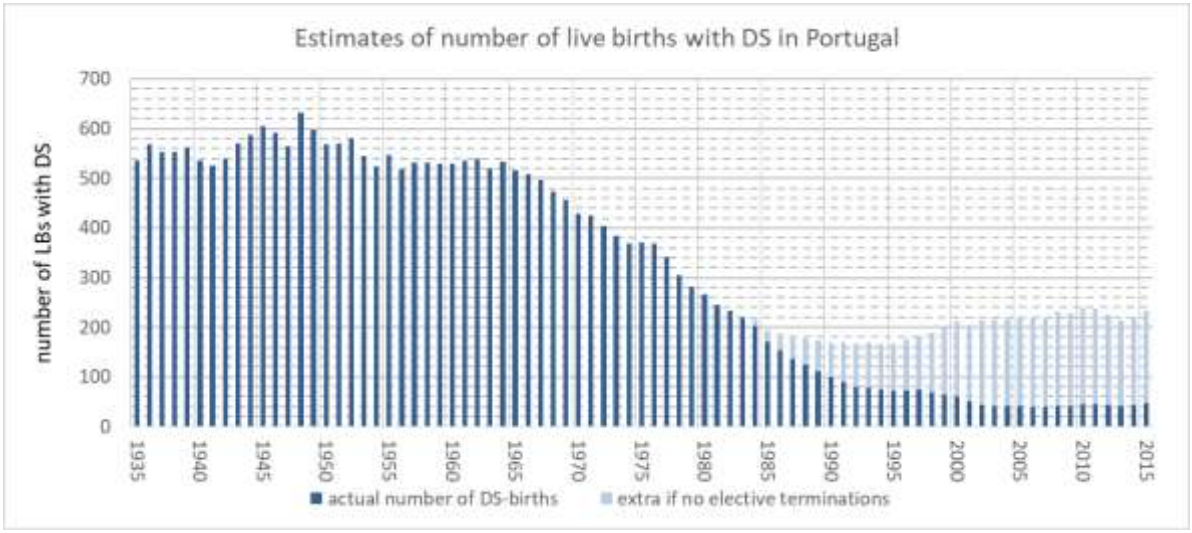


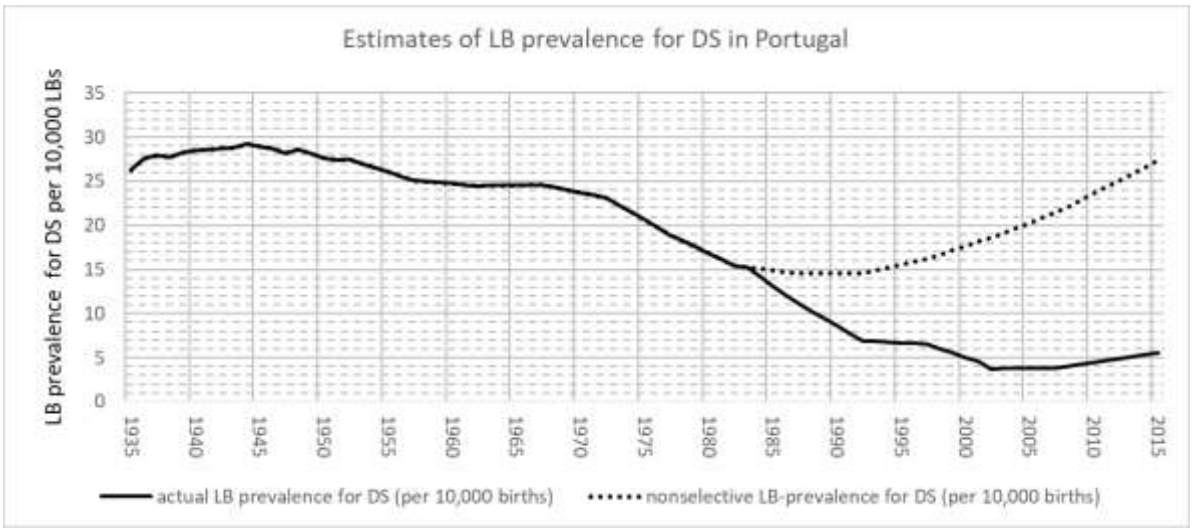


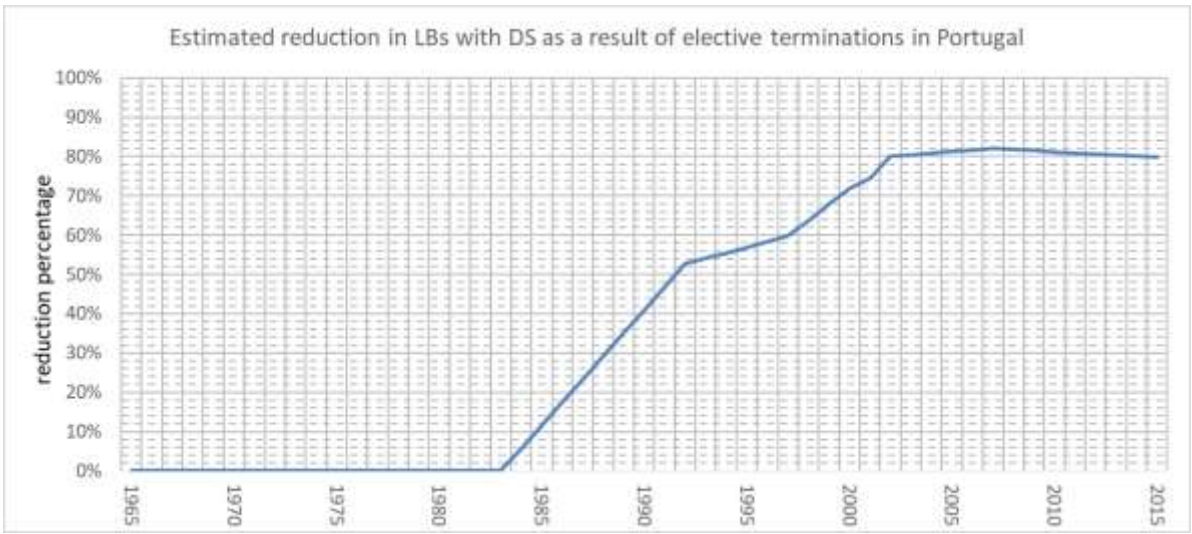

Estimated people with DS in North Macedonia, 1950-2015
900
800
700
600
500
400
300
200
100
0
4
3.5
3
2.5
2
1.5
1
0.5
0
185 207 197 183 179 187 191 190 209 282 358 440 522 606
200 245 266 284 307 335 355 367 397 478 557 633 707 780
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

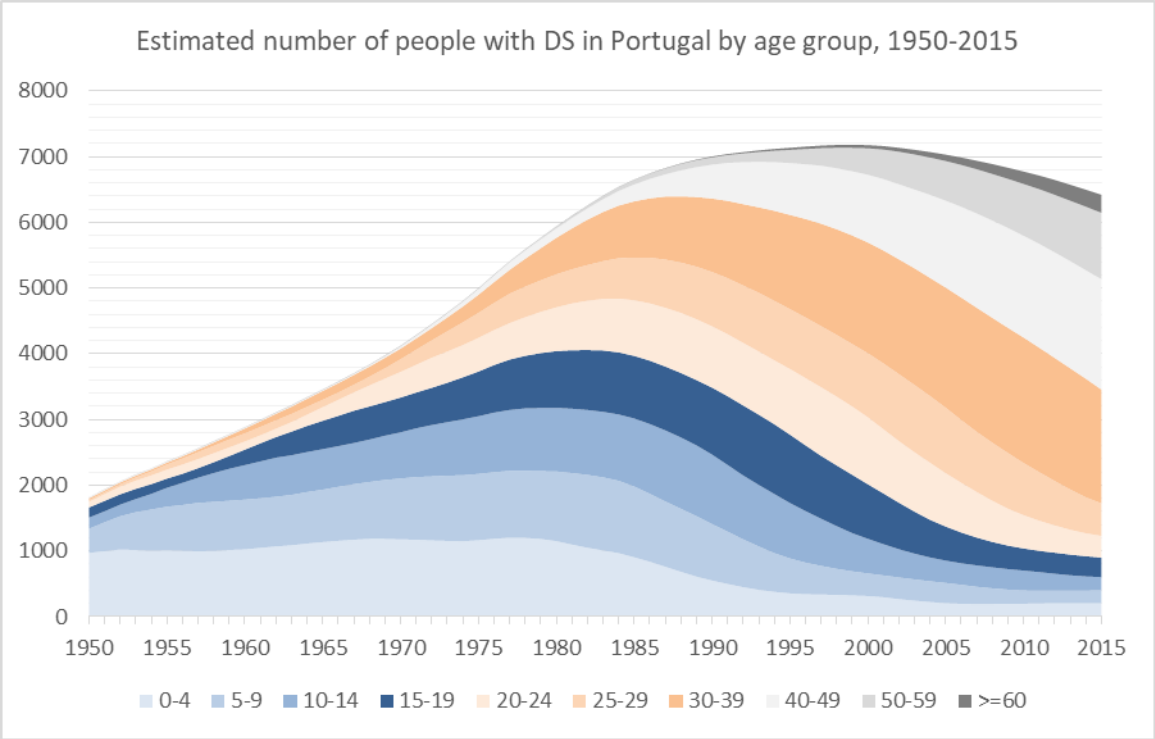

Estimated people with DS in North Macedonia by age group, as of 2015
model B
model D
120
100
80
60
40
20
0
10
9
8
7
6
5
4
3
2
1
0
105 94 90 87 76 49 28 25 20 13 8 7 4 1 0 0 0
105 94 91 92 89 73 58 52 42 33 25 17 8 2 0 0 0
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

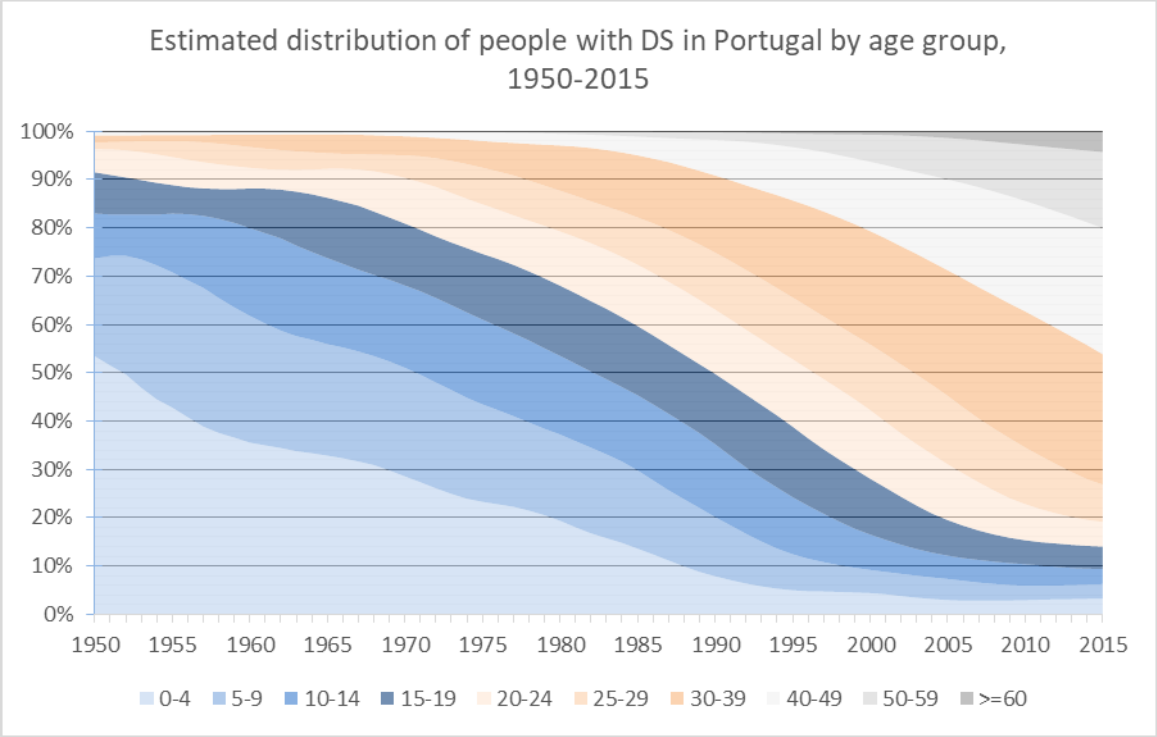
Portugal

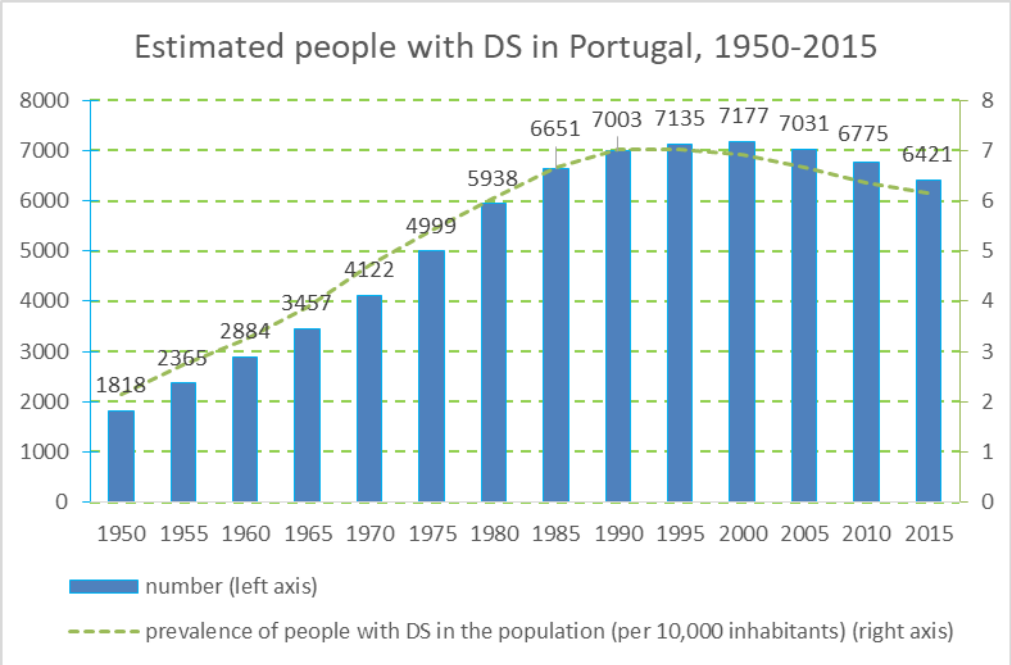

Estimates of number of live births with DS in Portugal
number of LBs with DS
700
600
500
400
300
200
100
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

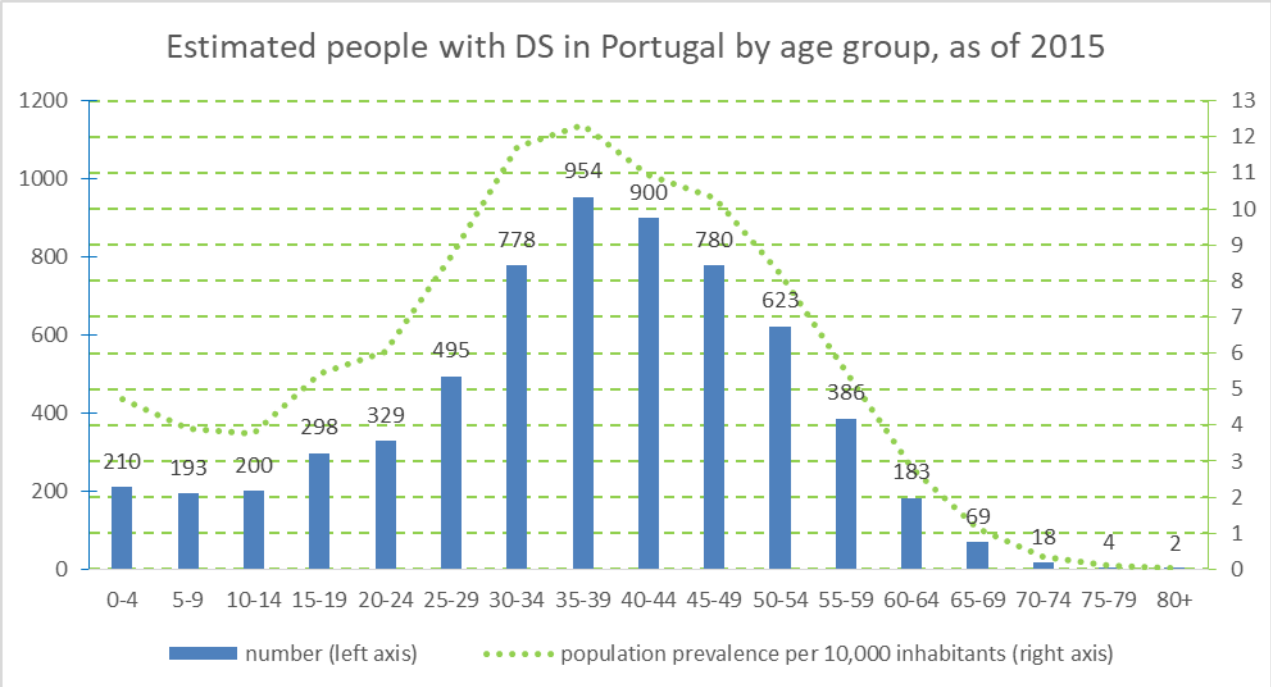

Estimates of LB prevalence for DS in Portugal
LB prevalence for DS per 10,000 LBs
35
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Portugal
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

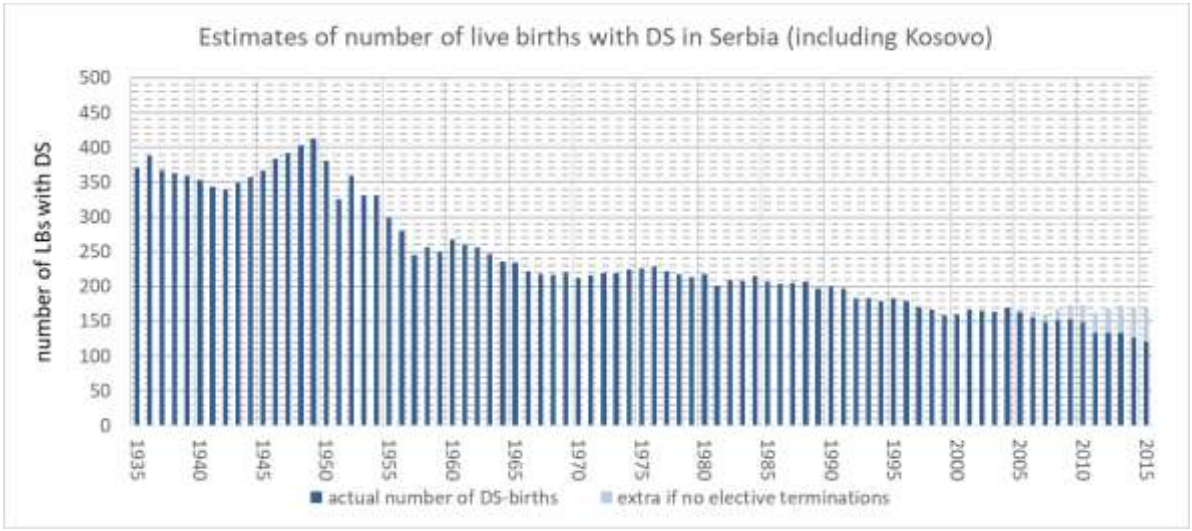

Estimated number of people with DS in Portugal by age group, 1950-2015
8000
7000
6000
5000
4000
3000
2000
1000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

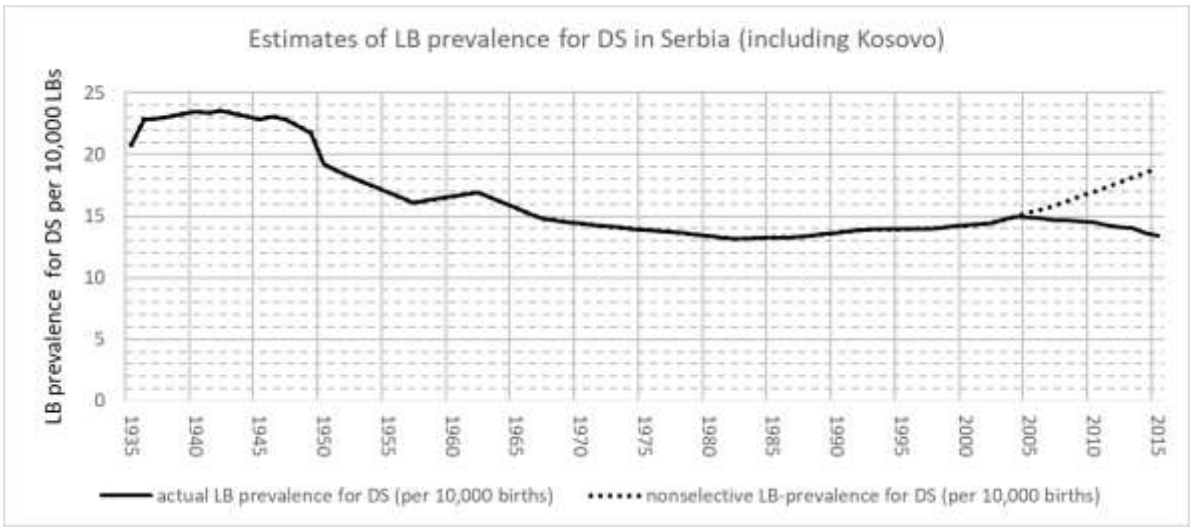

Estimated distribution of people with DS in Portugal by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

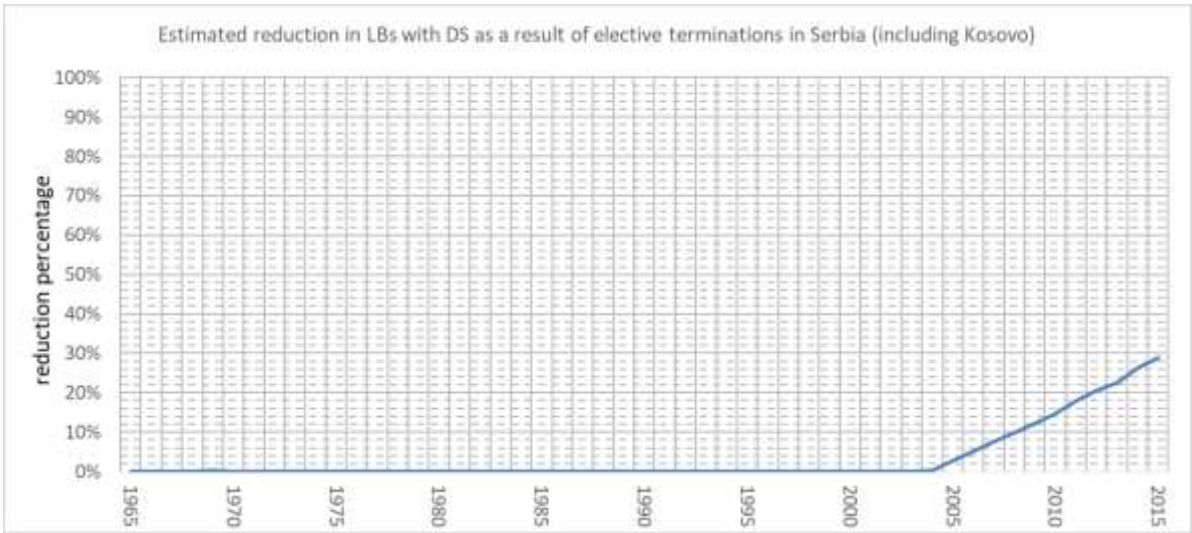

Estimated people with DS in Portugal, 1950-2015
8000
7000
6000
5000
4000
3000
2000
1000
0
8
7
6
5
4
3
2
1
0
1818
2365
2884
3457
4122
4999
5938
6651
7003
7135
7177
7031
6775
6421
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Portugal by age group, as of 2015
1200
1000
800
600
400
200
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
210
193
200
298
329
495
778
954
900
780
623
386
183
69
18
4
2
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

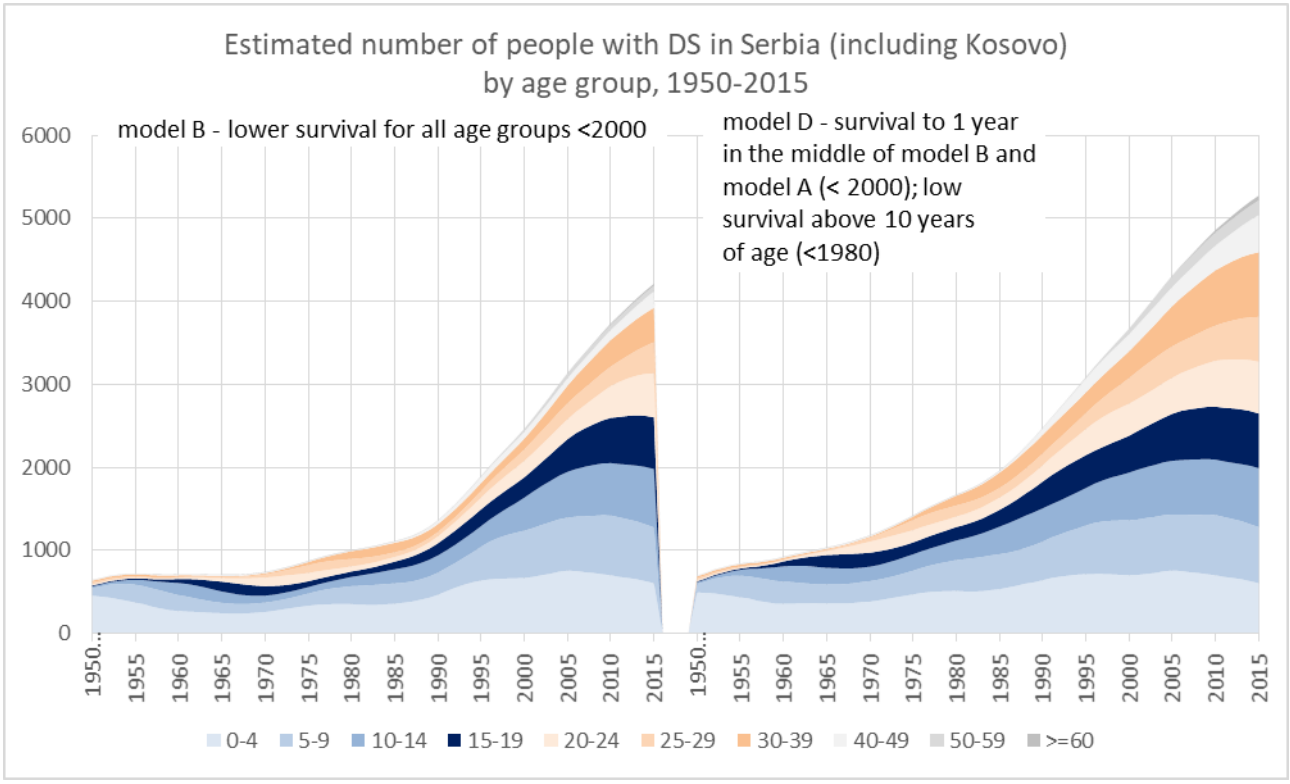
Serbia (including Kosovo)

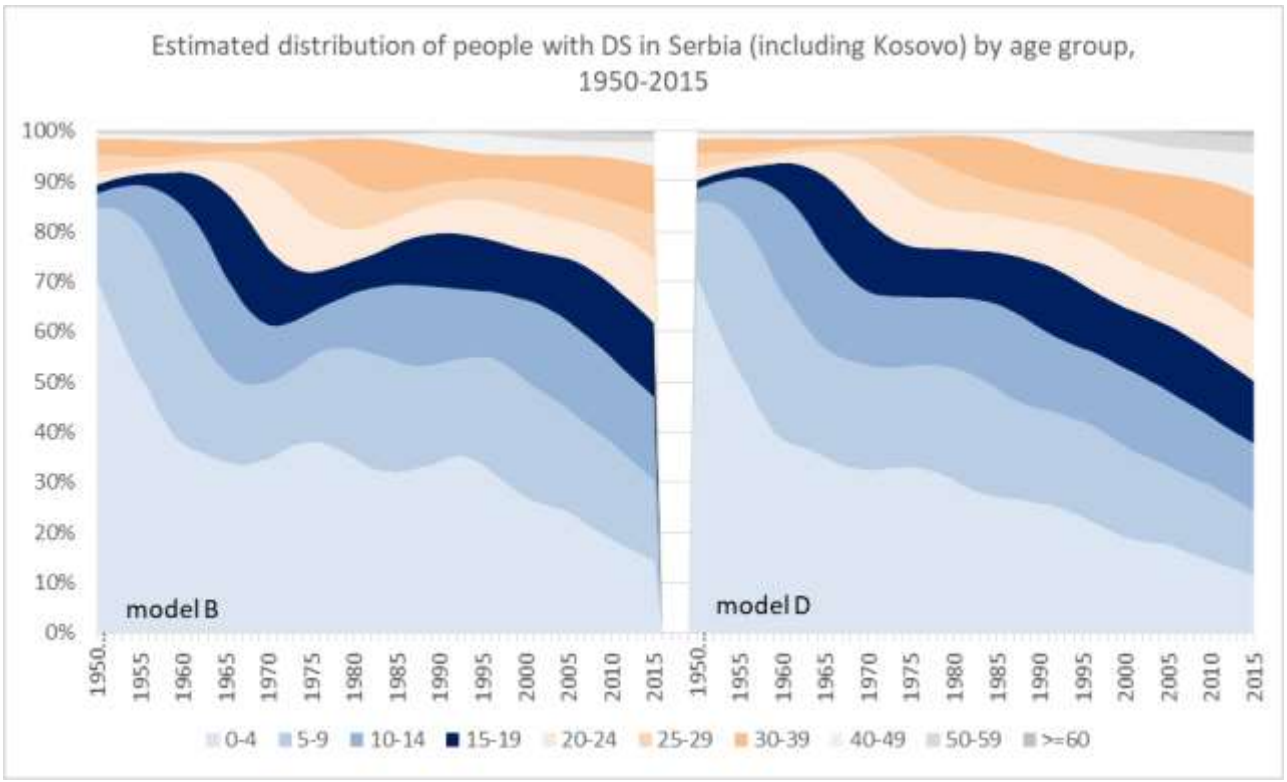




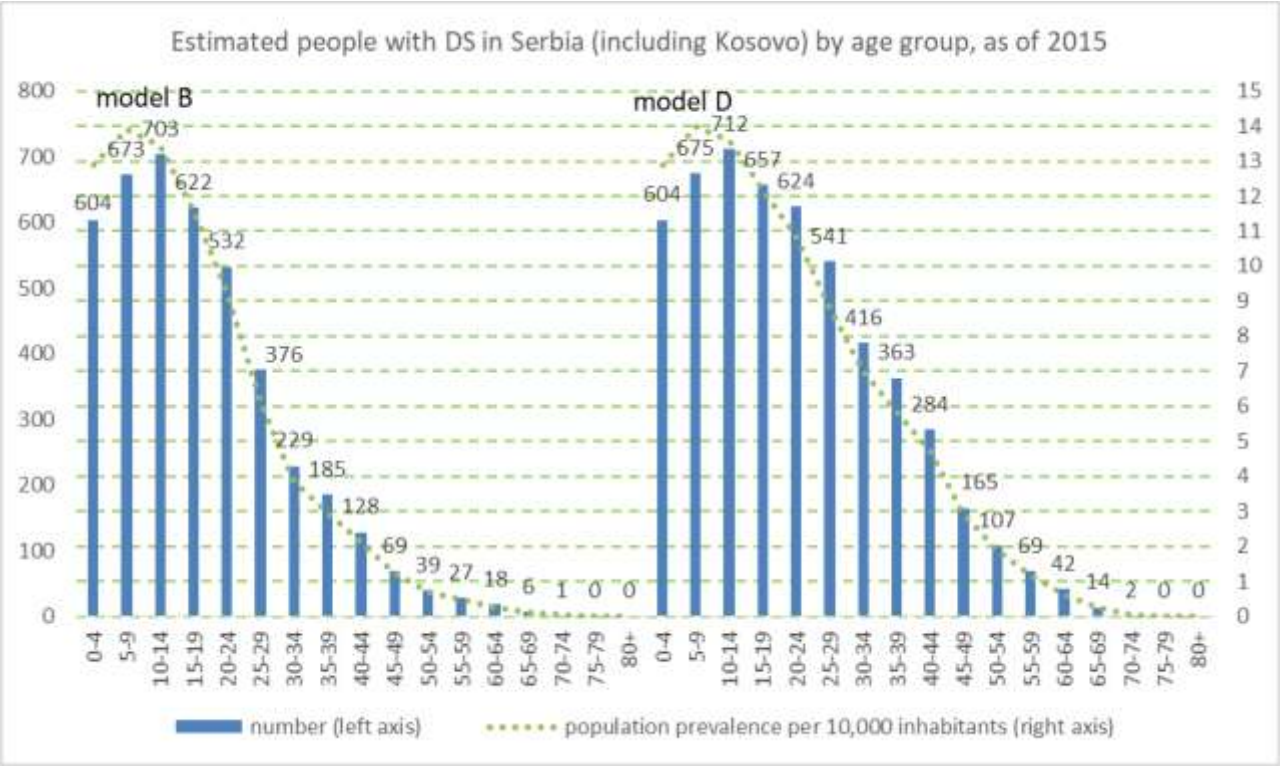


Model A projects 6,483 people with DS alive in 2015, which corresponds to a population prevalence of 7.3 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 6,261 (7.1 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Serbia, Model D seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics (see S5C).

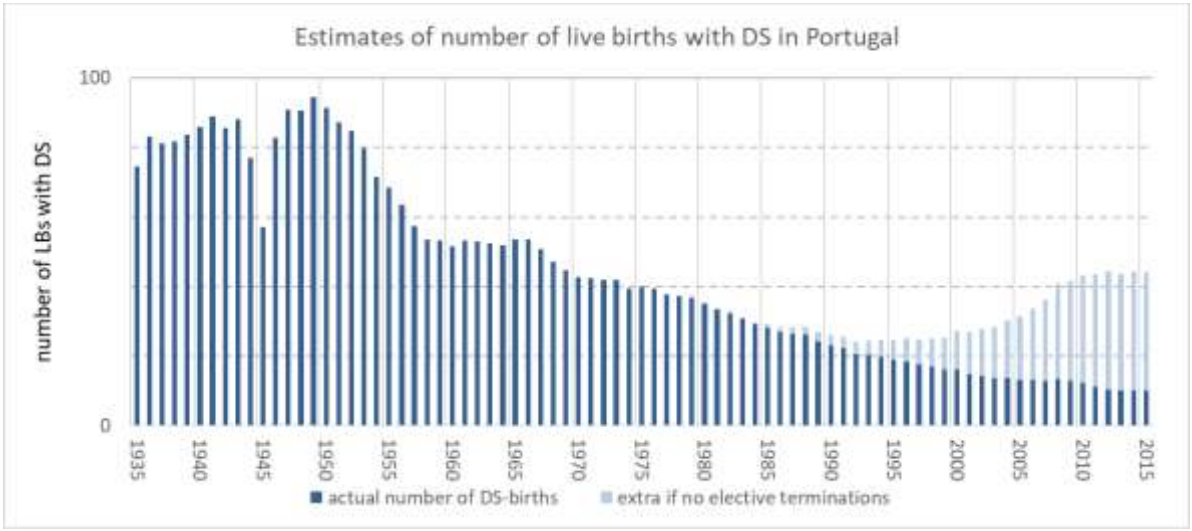


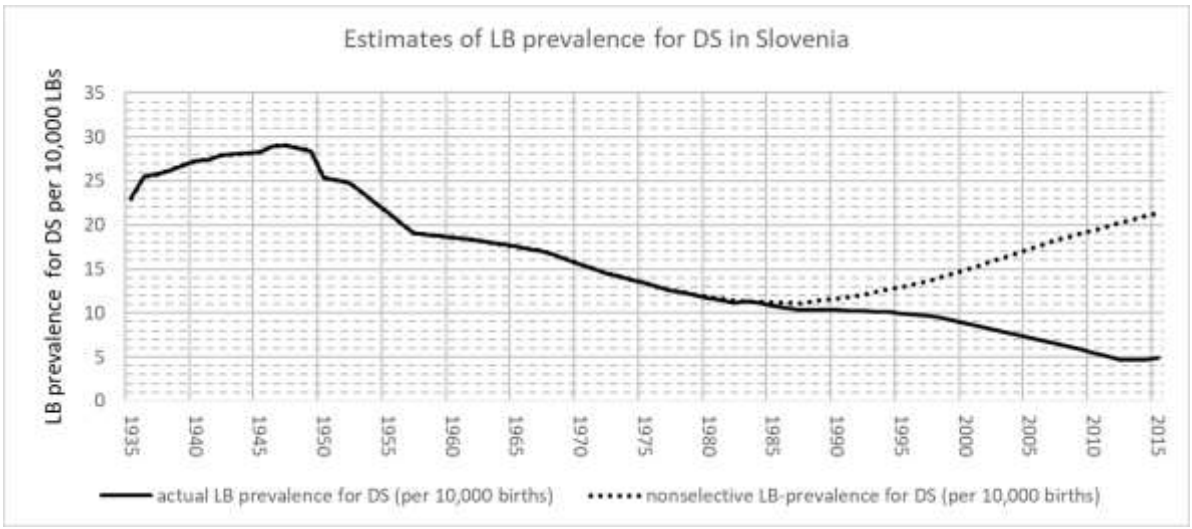


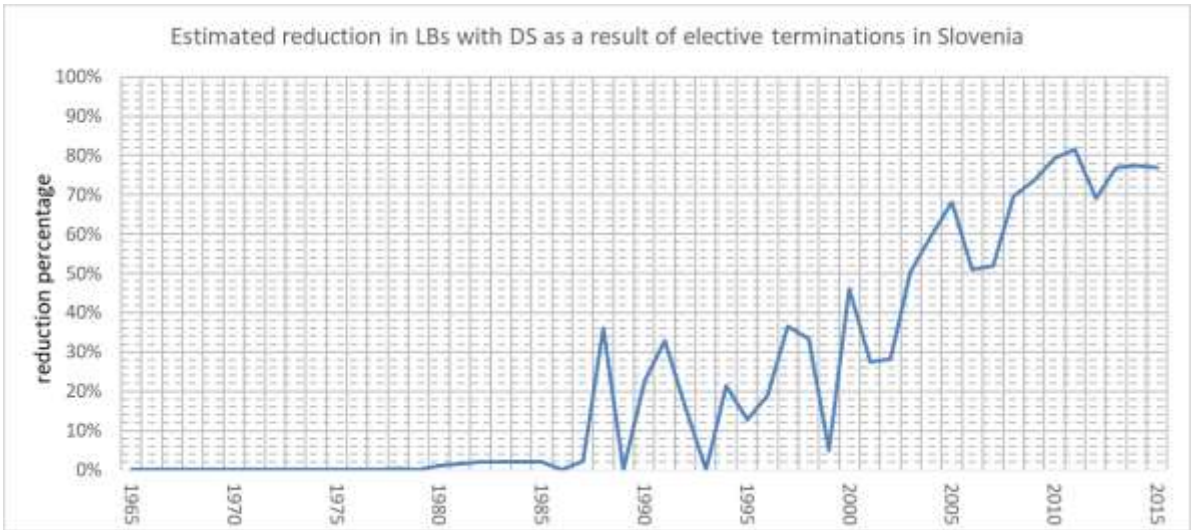

Estimated people with DS in Serbia (including Kosovo), 1950-2015
6000
5000
4000
3000
2000
1000
0
7
6
5
4
3
2
1
0
645 722 713 708 741 872 1004 1111 1361 1896 2462 3133 3734 4213
696 842 923 1036 1180 1421 1673 1960 2477 3088 3672 4311 4861 5275
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Serbia (including Kosovo) by age group, as of 2015
model B
model D
800
700
600
500
400
300
200
100
0
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
604 673 703 622 532 376 229 185 128 69 39 27 18 6 1 0 0
604 675 712 657 624 541 416 363 284 165 107 69 42 14 2 0 0
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Slovenia

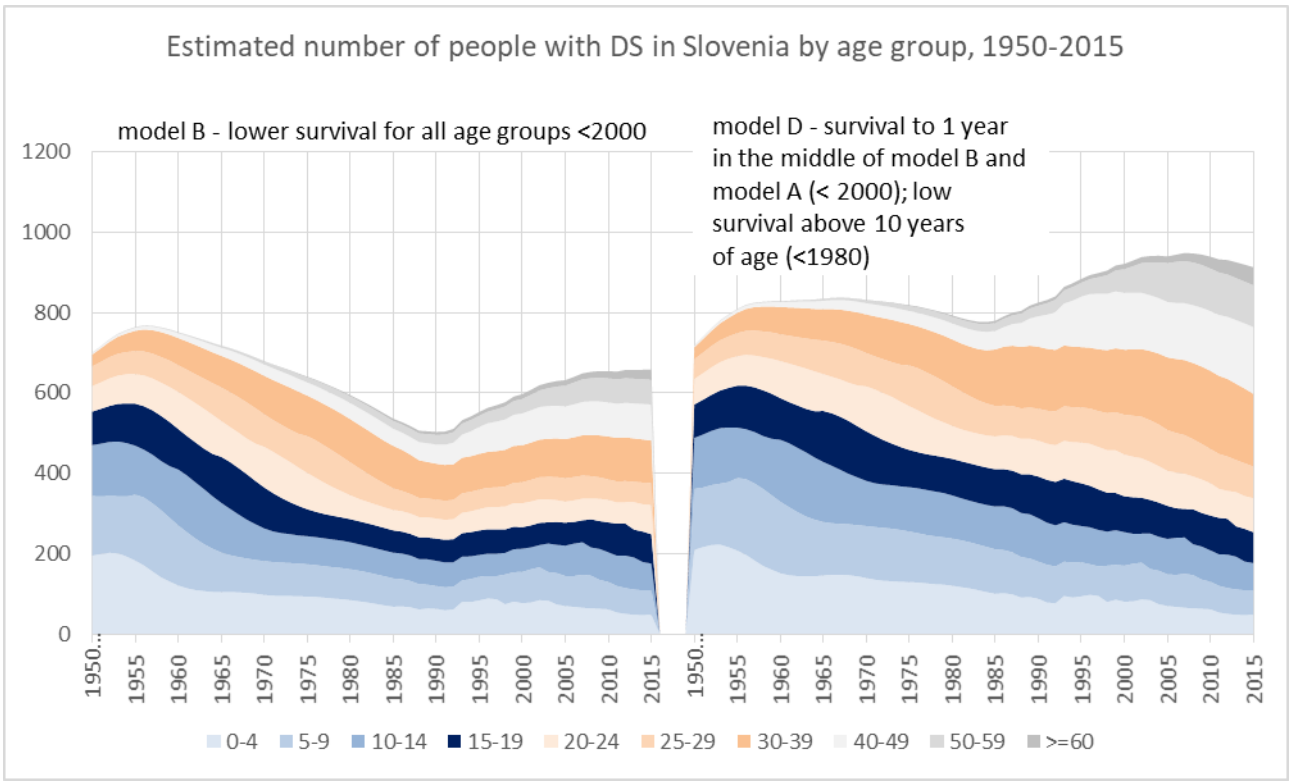


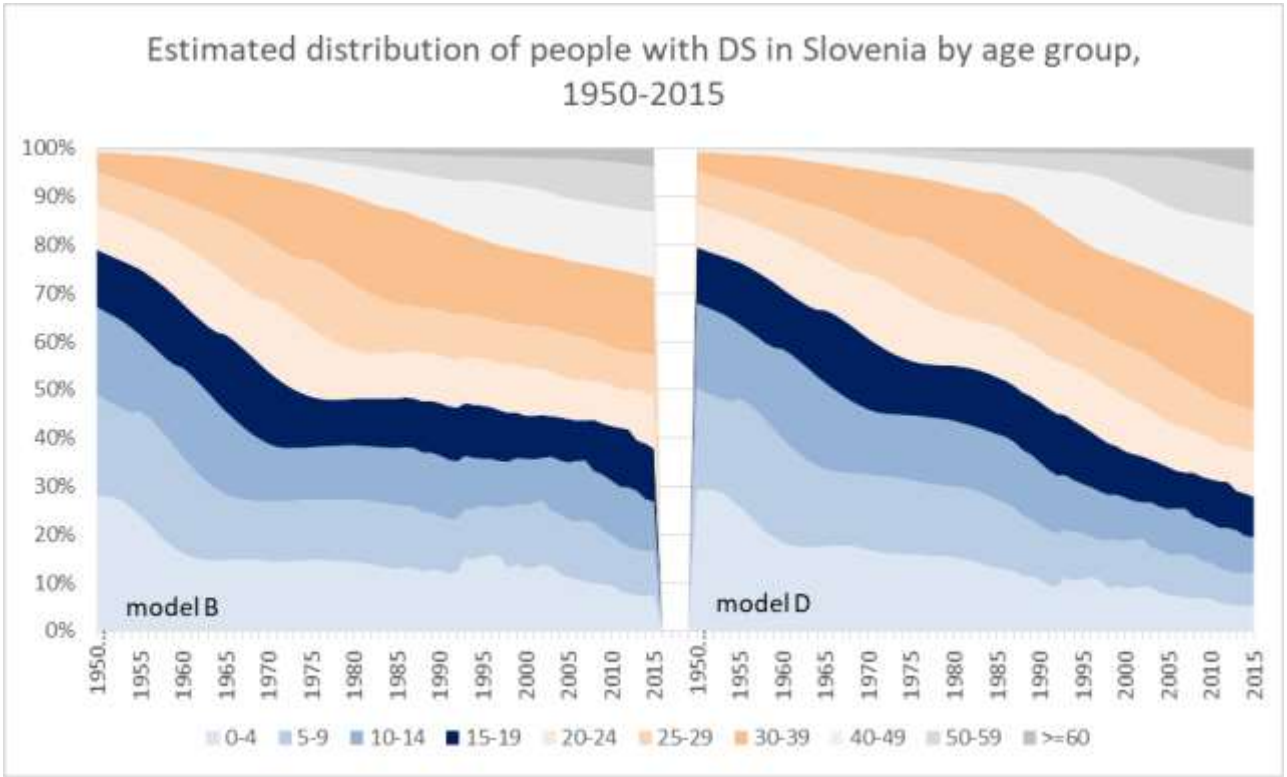


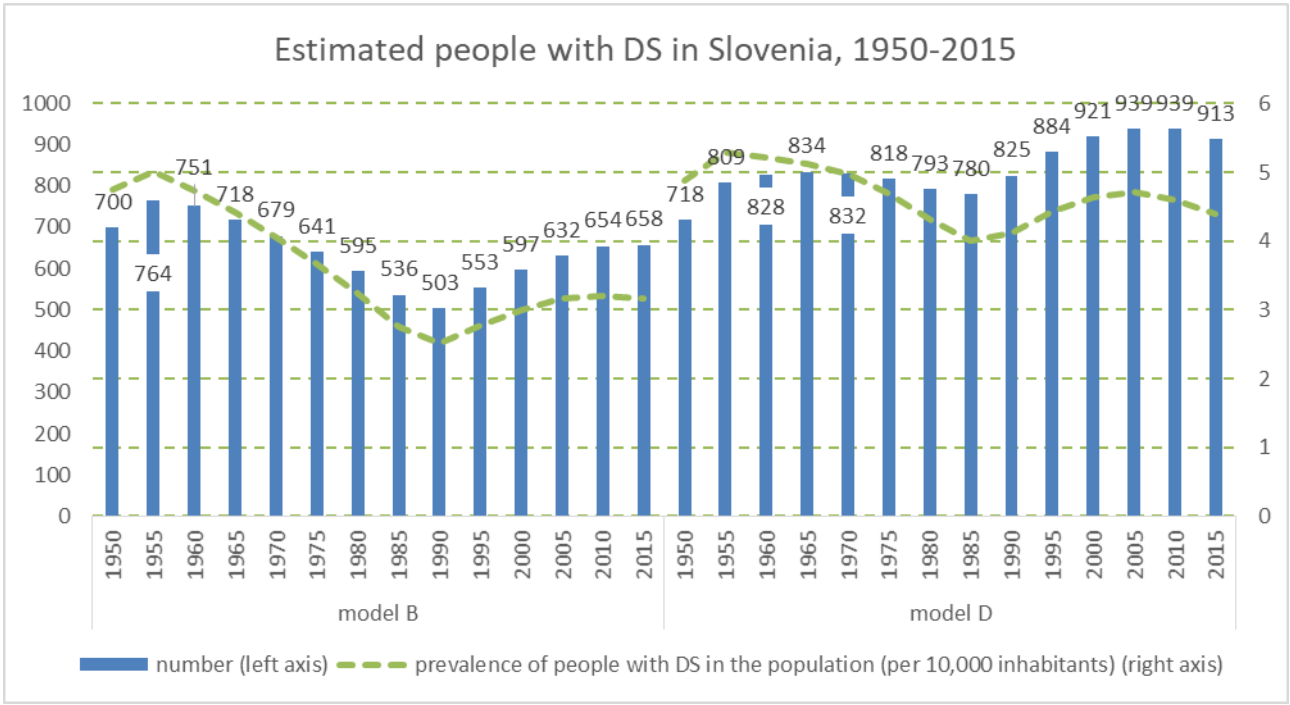


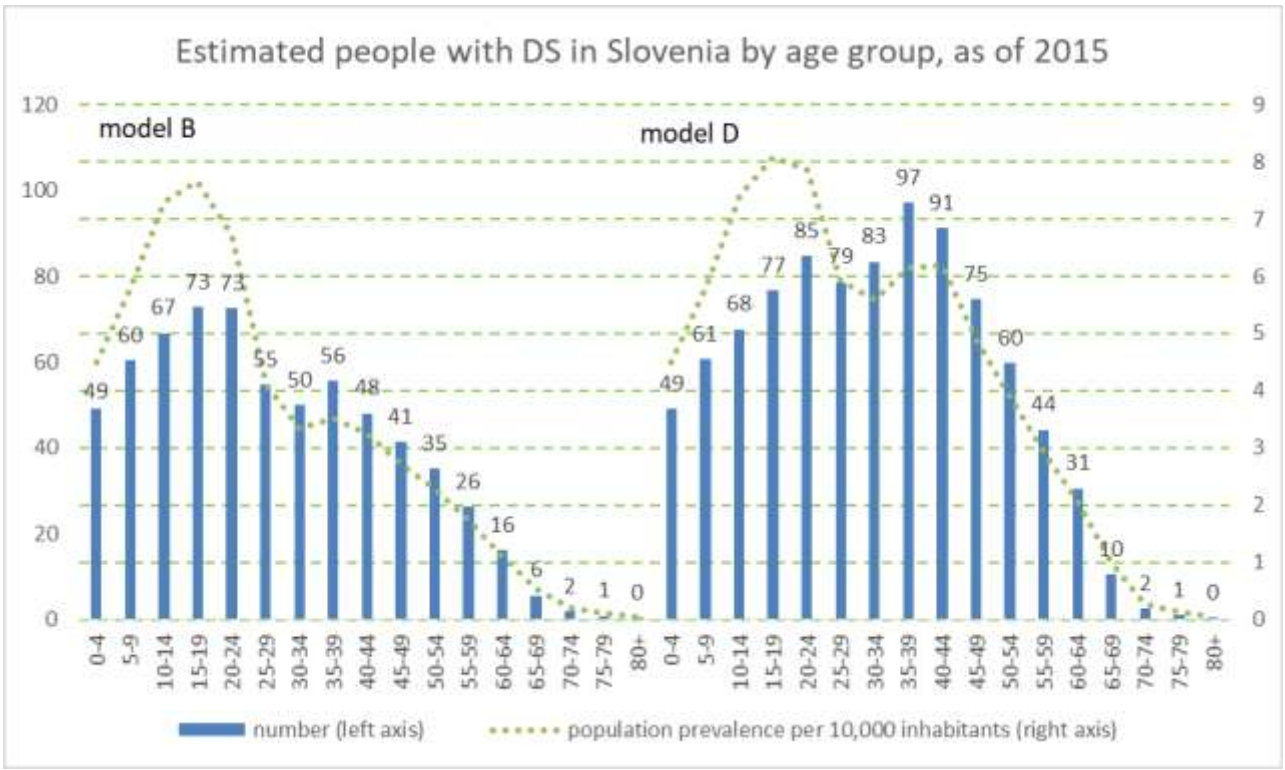
In the graph above, negative reduction percentages (if nonselective prevalence is smaller than actual prevalence) have been set to zero after 1985. This was the case for 1986 (-21%), 1989 (-3%), 1993 (-50%). This can be a result of some random fluctuation in a relatively small population.

Model A projects 1,308 people with DS alive in 2015, which corresponds to a population prevalence of 6.3 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 1,126 (5.4 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Slovenia, Model D seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics for 2005–2015 (see S5C).

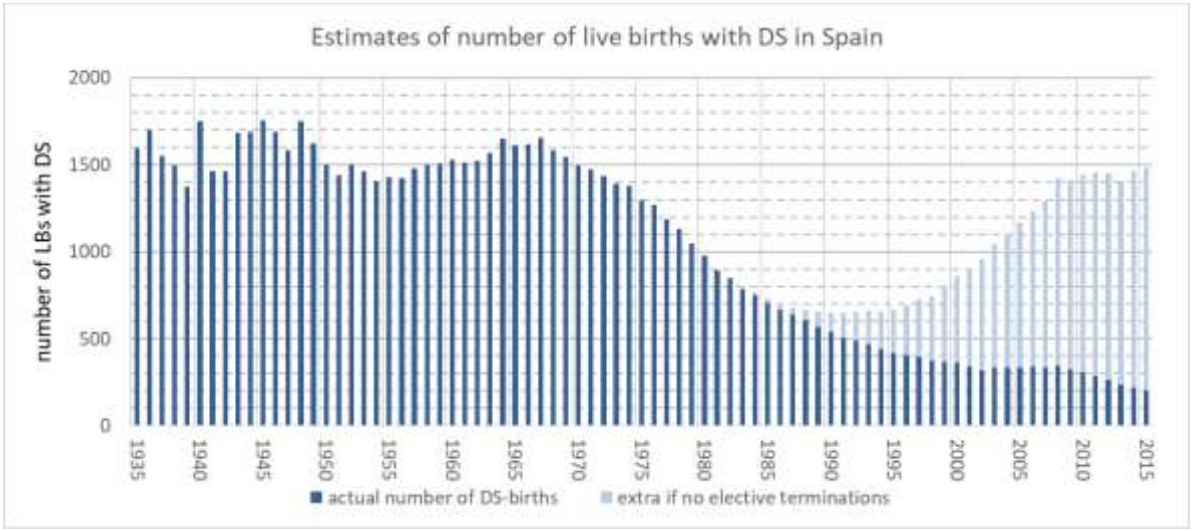


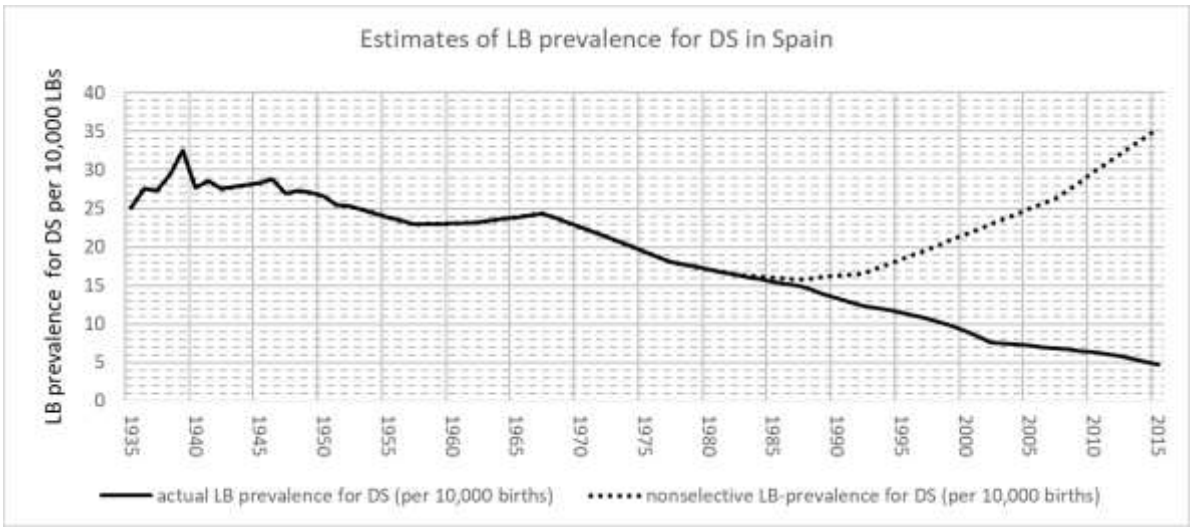


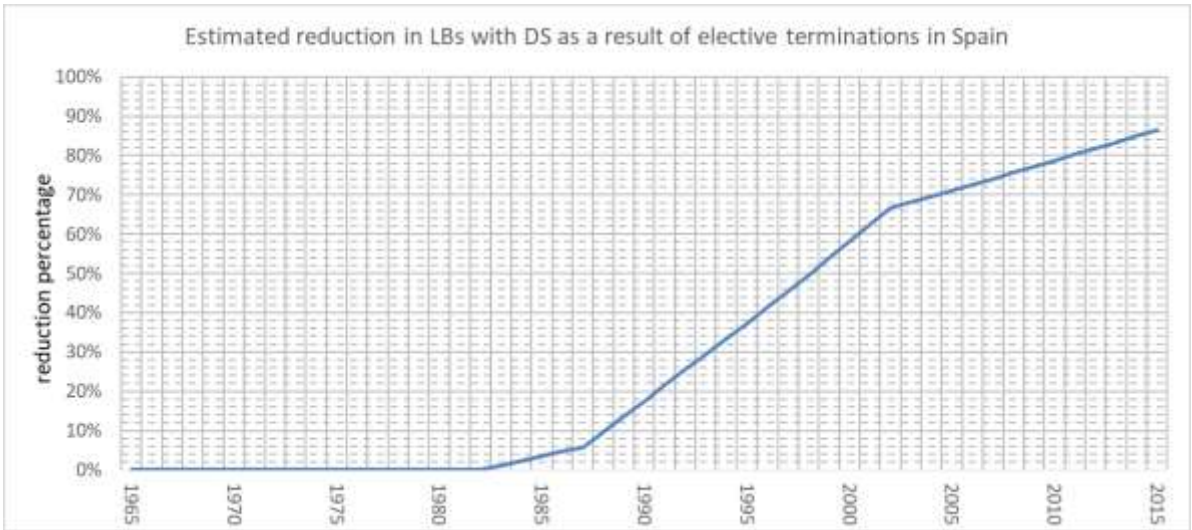

Estimated people with DS in Slovenia, 1950-2015
1000
900
800
700
600
500
400
300
200
100
0
6
5
4
3
2
1
0
700
764
751
718
679
641
595
536
503
553
597
632
654
658
718
809
828
834
832
818
793
780
825
884
921
939
939
913
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

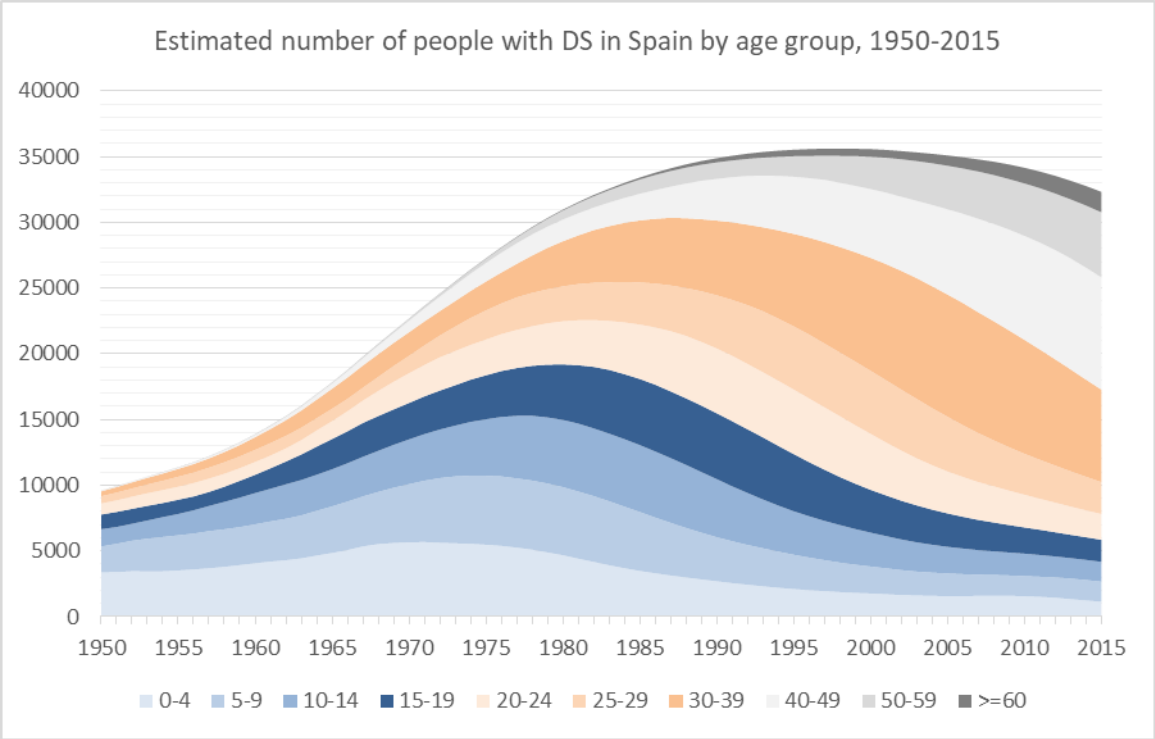

Estimated people with DS in Slovenia by age group, as of 2015
model B
model D
120
100
80
60
40
20
0
9
8
7
6
5
4
3
2
1
0
49
60
67
73
73
55
50
56
48
41
35
26
16
6
2
1
0
49
61
68
77
85
79
83
97
91
75
60
44
31
10
2
1
0
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

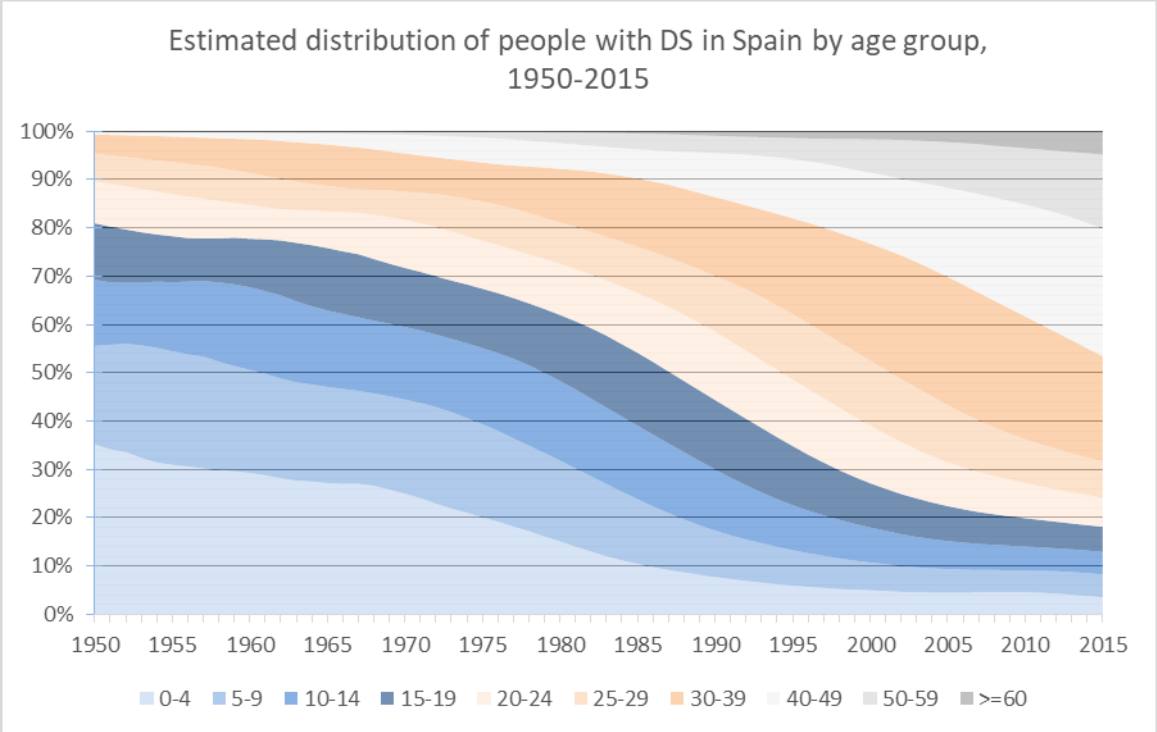
Spain

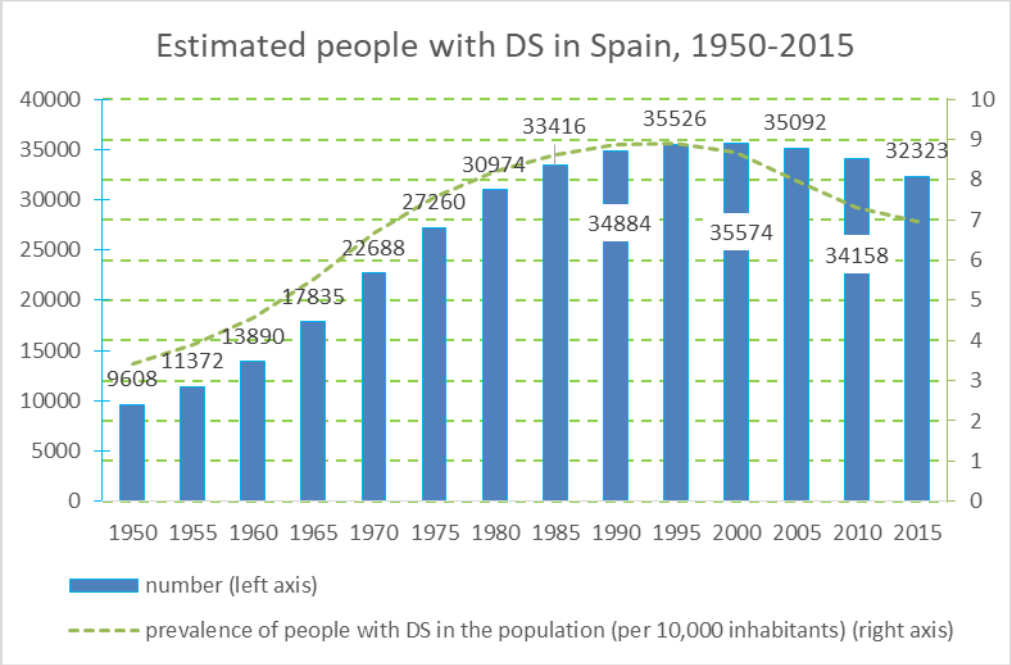

Estimates of number of live births with DS in Spain
number of LBs with DS
2000
1500
1000
500
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

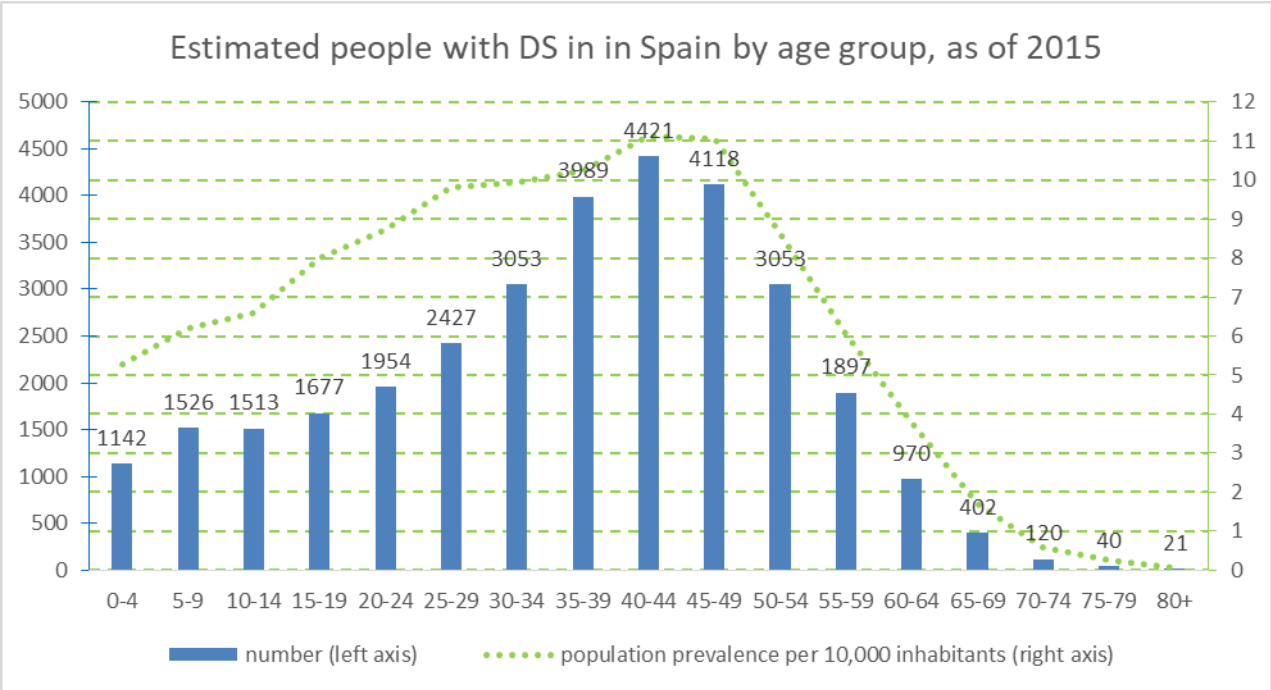

Estimates of LB prevalence for DS in Spain
LB prevalence for DS per 10,000 LBs
40
35
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)


Estimated reduction in LBs with DS as a result of elective terminations in Spain
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015


Estimated number of people with DS in Spain by age group, 1950-2015
40000
35000
30000
25000
20000
15000
10000
5000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

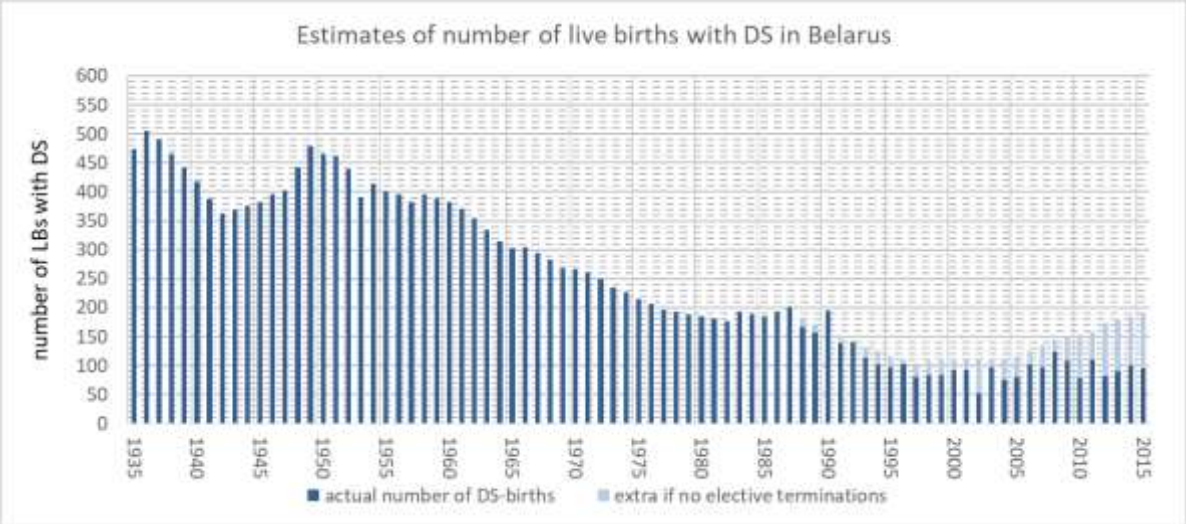

Estimated distribution of people with DS in Spain by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

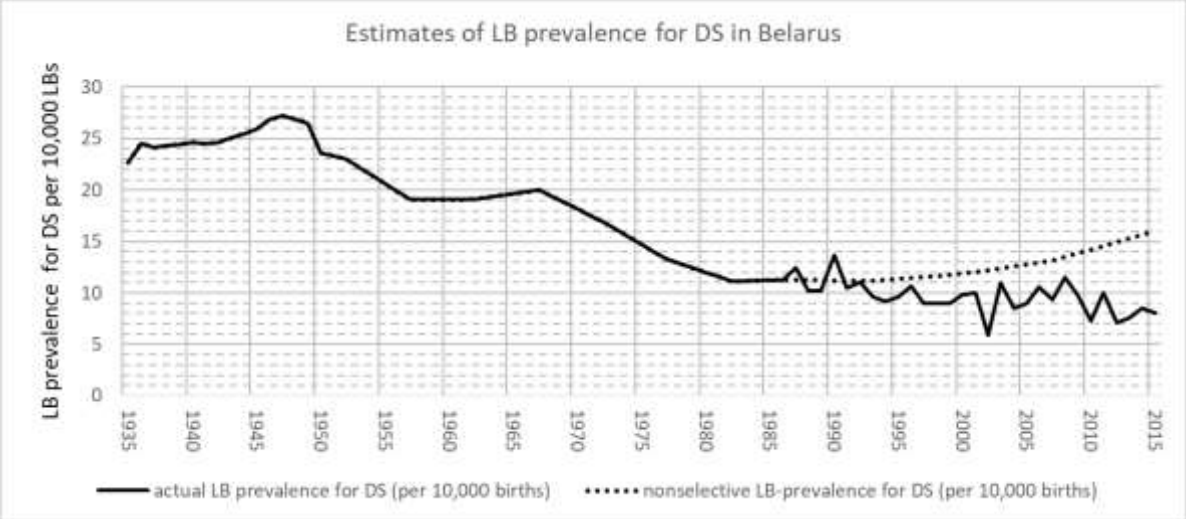

Estimated people with DS in Spain, 1950-2015
40000
35000
30000
25000
20000
15000
10000
5000
0
10
9
8
7
6
5
4
3
2
1
0
9608
11372
13890
17835
22688
27260
30974
33416
34884
35526
35574
35092
34158
32323
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

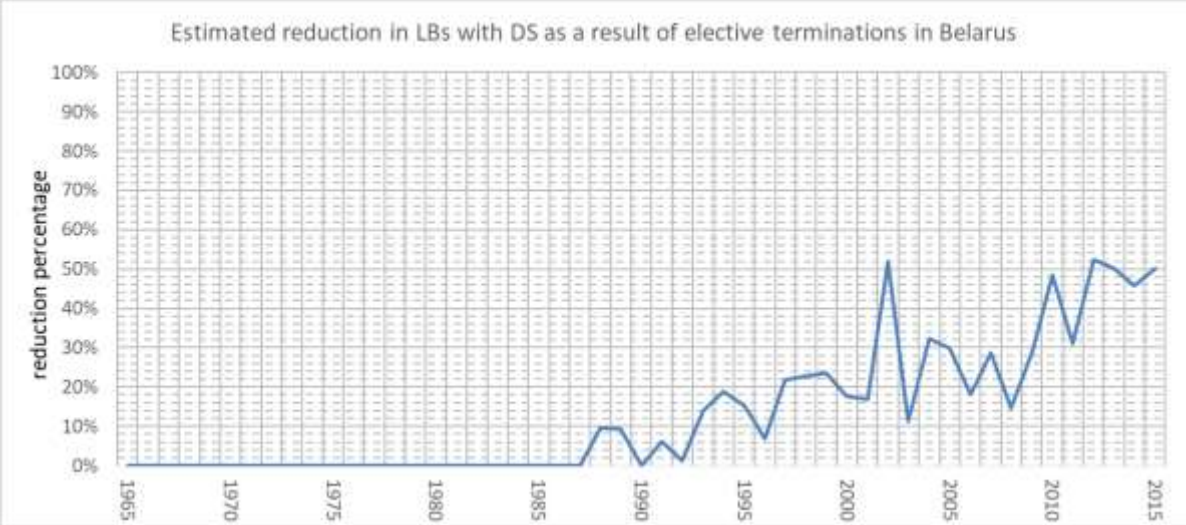

Estimated people with DS in in Spain by age group, as of 2015
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
12
11
10
9
8
7
6
5
4
3
2
1
0
1142
1526
1513
1677
1954
2427
3053
3989
4421
4118
3053
1897
970
402
120
40
21
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Eastern Europe

Belarus

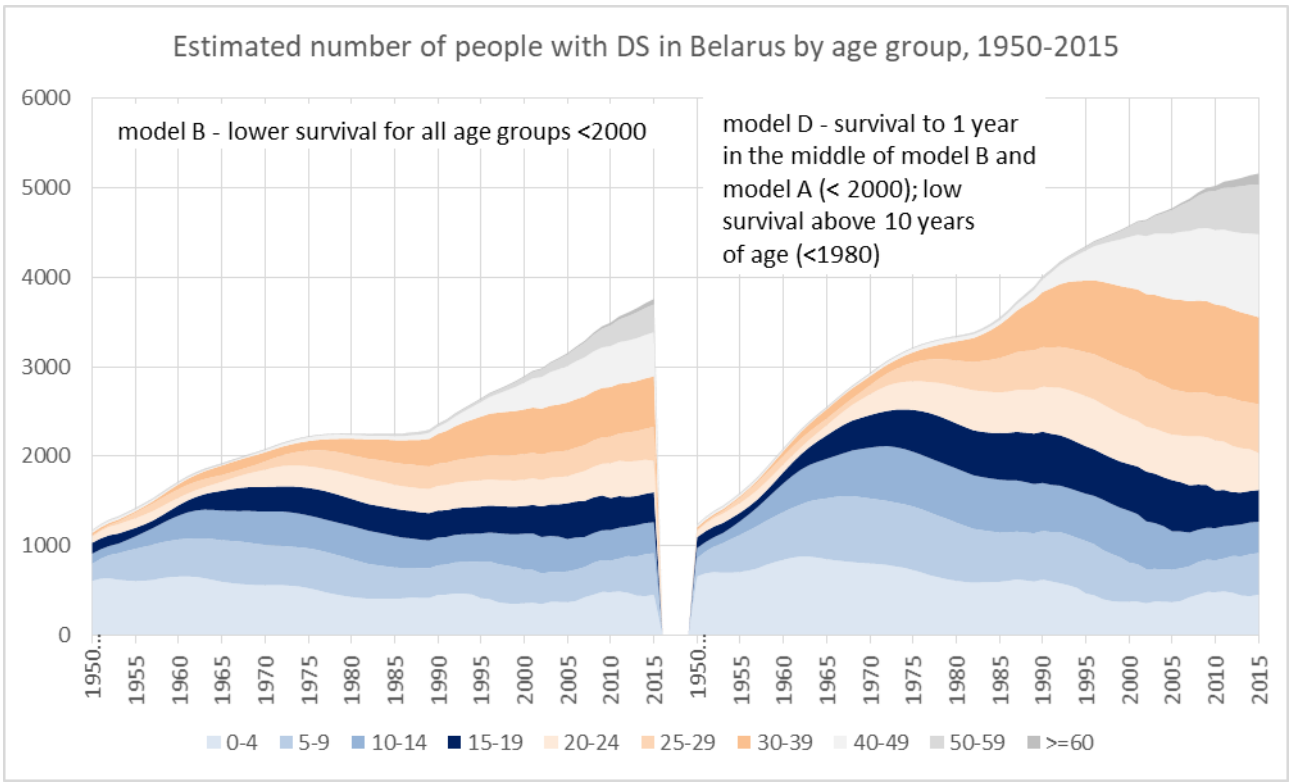


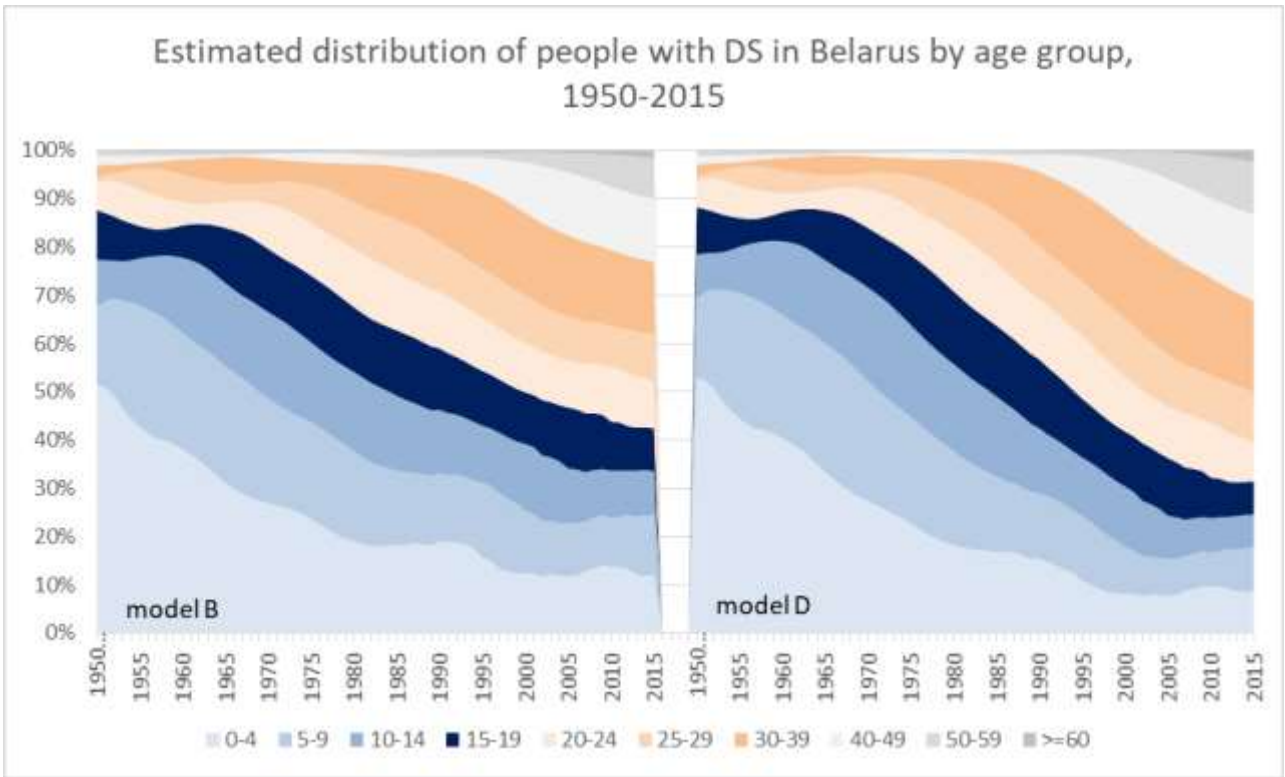


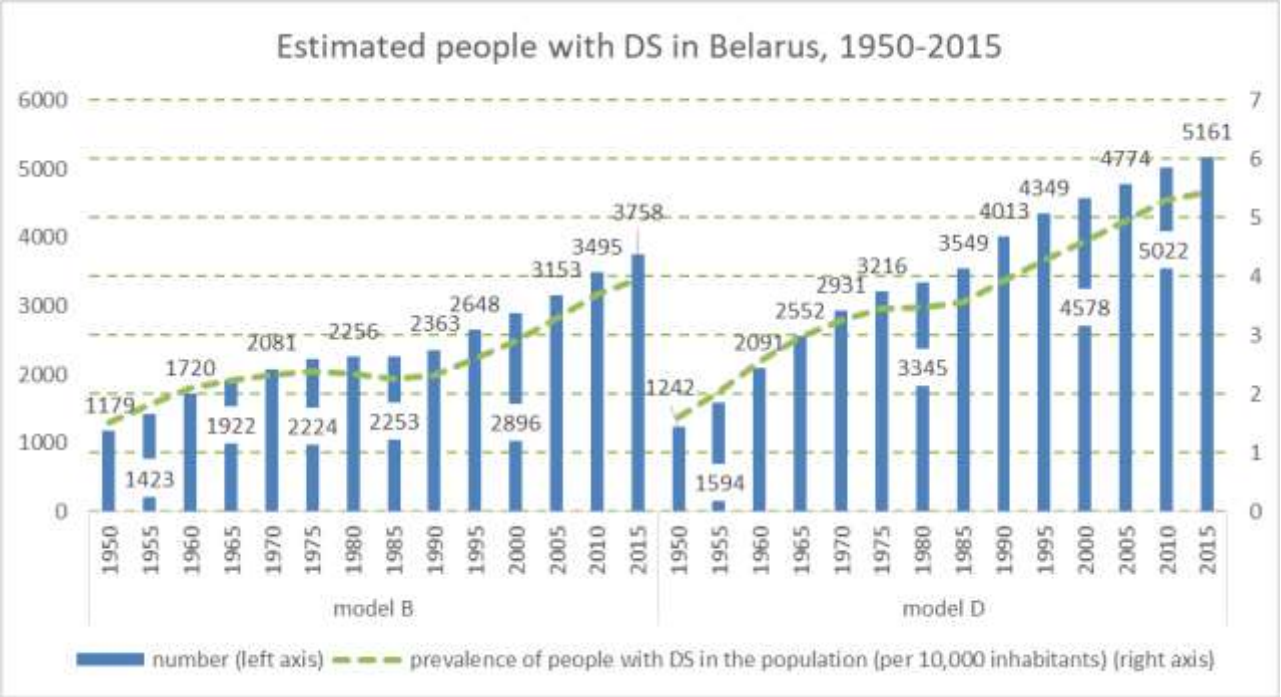


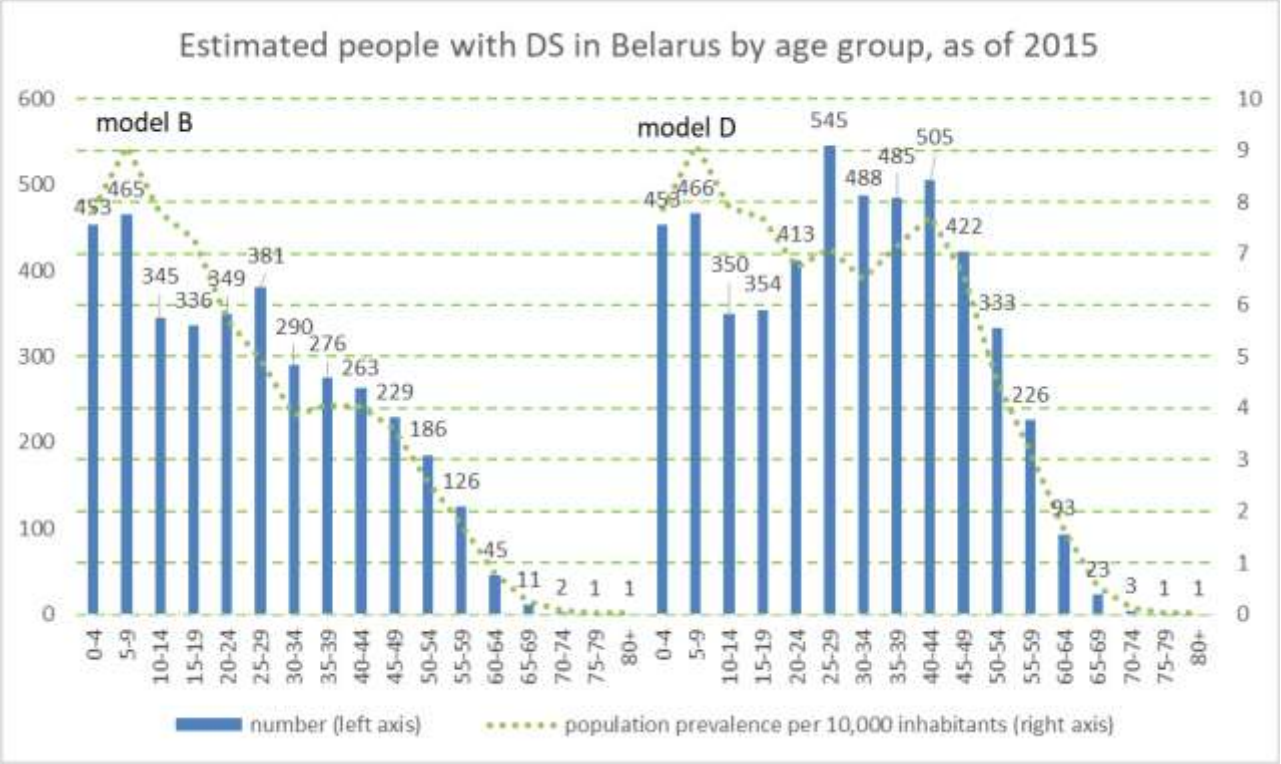
Negative reduction percentages have been set to zero.

Model A projects 7,176 people with DS alive in 2015, which corresponds to a population prevalence of 7.6 people with DS per 10,000 inhabitants. Model C projects 6,385 (6.7 per 10,000). However, we consider Model B or Model D more likely for former East bloc countries. For Belarus, there is no info on deaths with DS from national statistics.

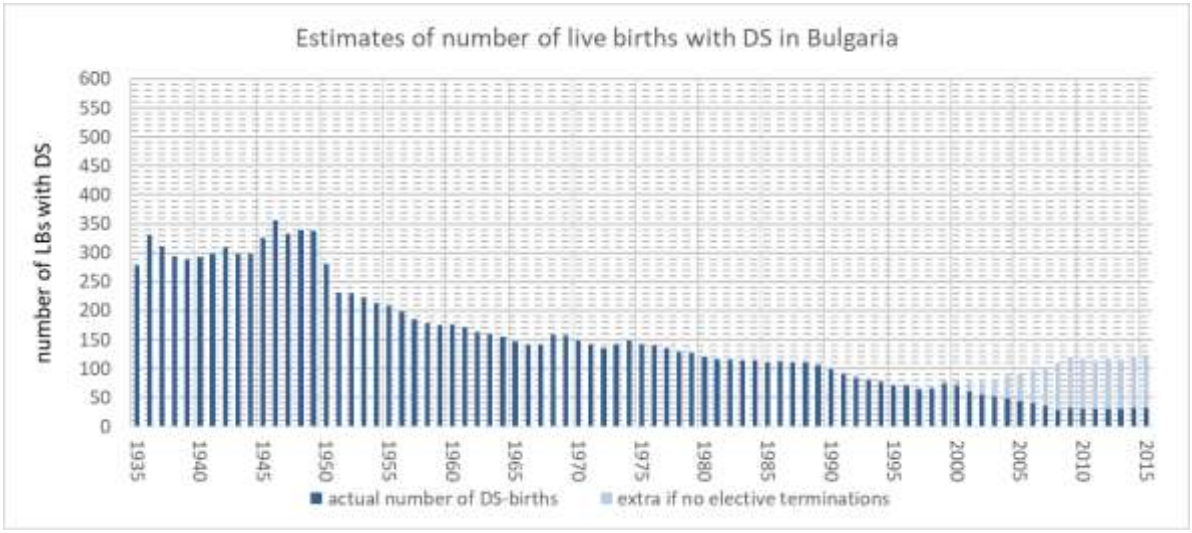


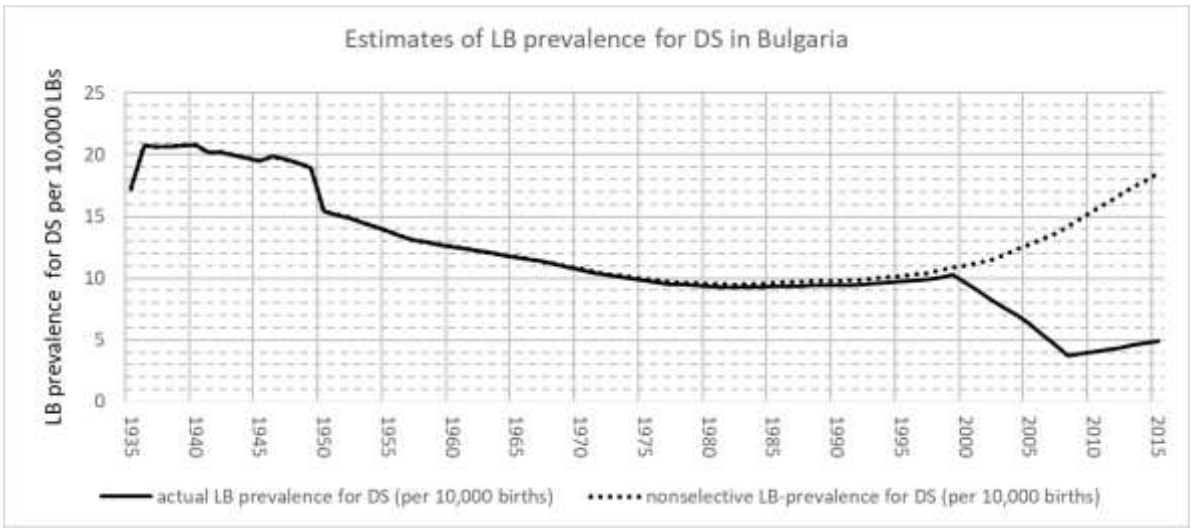


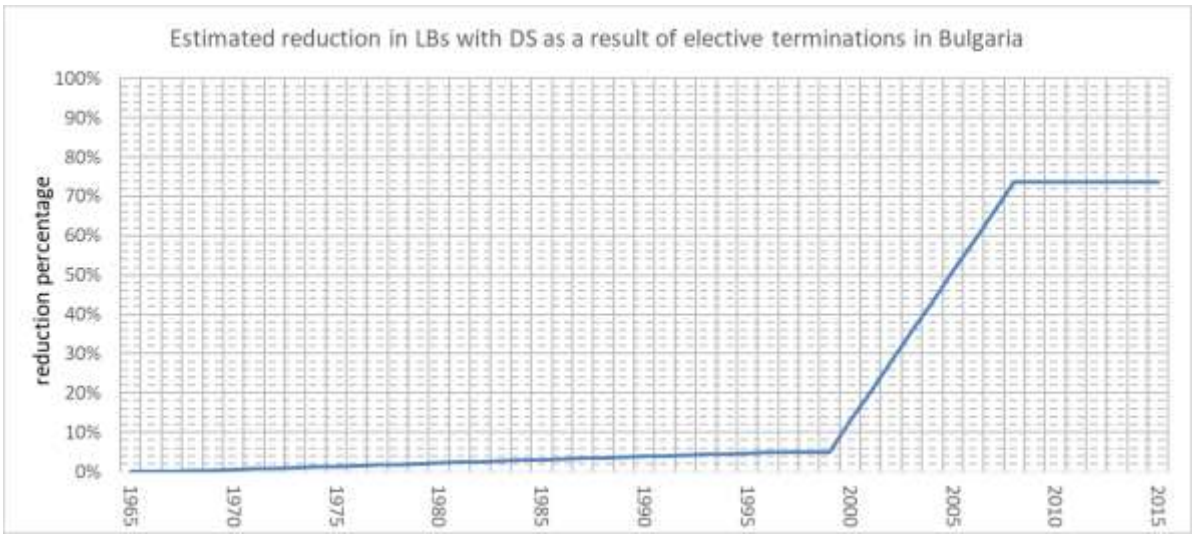

Estimated people with DS in Belarus, 1950-2015
6000
5000
4000
3000
2000
1000
0
7
6
5
4
3
2
1
0
1179
1423
1720
1922
2081
2224
2256
2253
2363
2648
2896
3153
3495
3758
1242
1594
2091
2552
2931
3216
3345
3549
4013
4349
4578
4774
5022
5161
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Belarus by age group, as of 2015
600
500
400
300
200
100
0
10
9
8
7
6
5
4
3
2
1
0
model B
model D
453
465
345
336
349
381
290
276
263
229
186
126
45
11
2
1
1
453
466
350
354
413
545
488
485
505
422
333
226
93
23
3
1
1
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

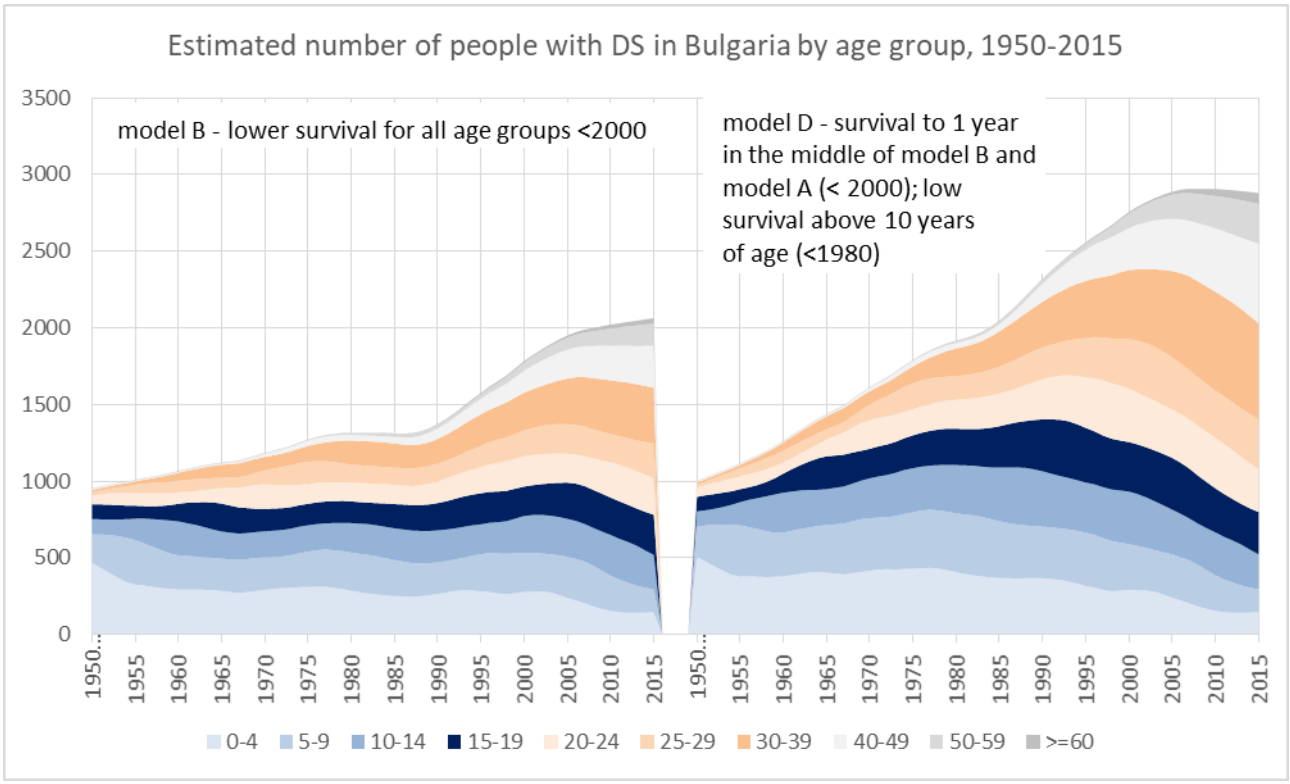
Bulgaria

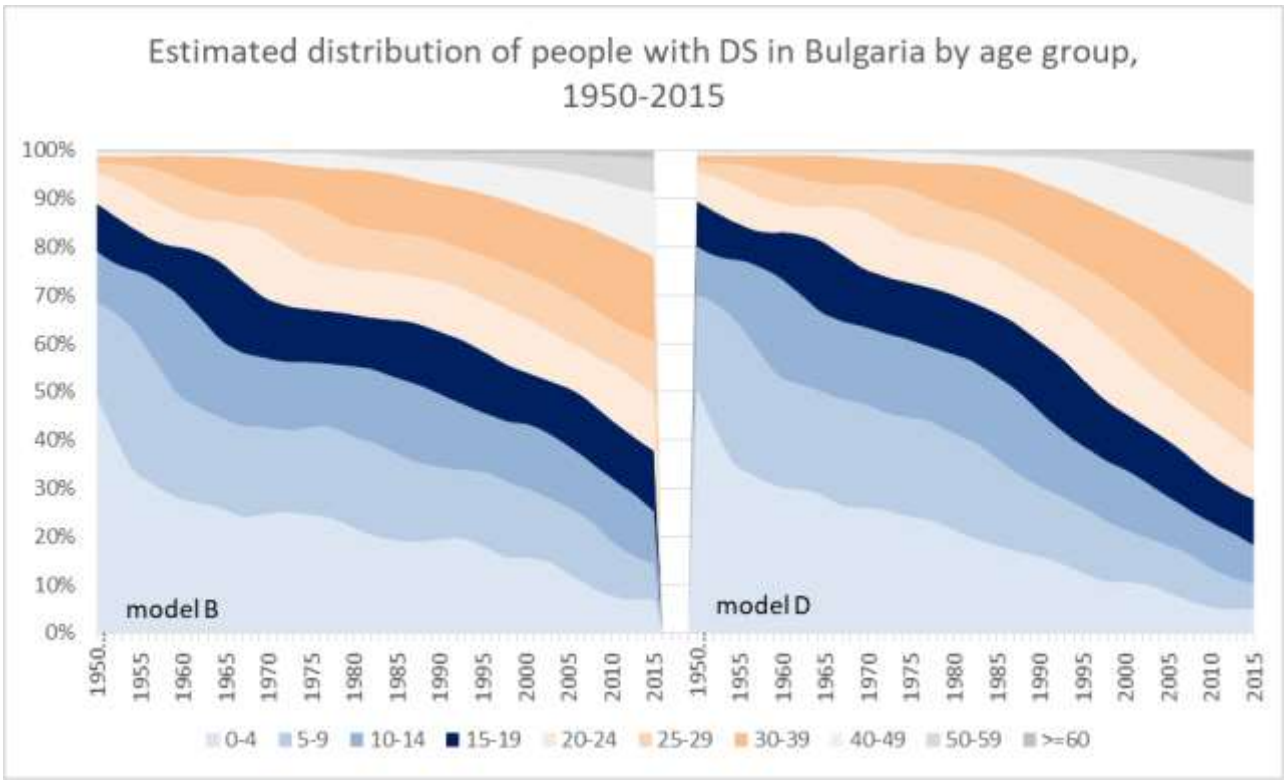

Estimates of number of live births with DS in Bulgaria
number of LBs with DS
600
550
500
450
400
350
300
250
200
150
100
50
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

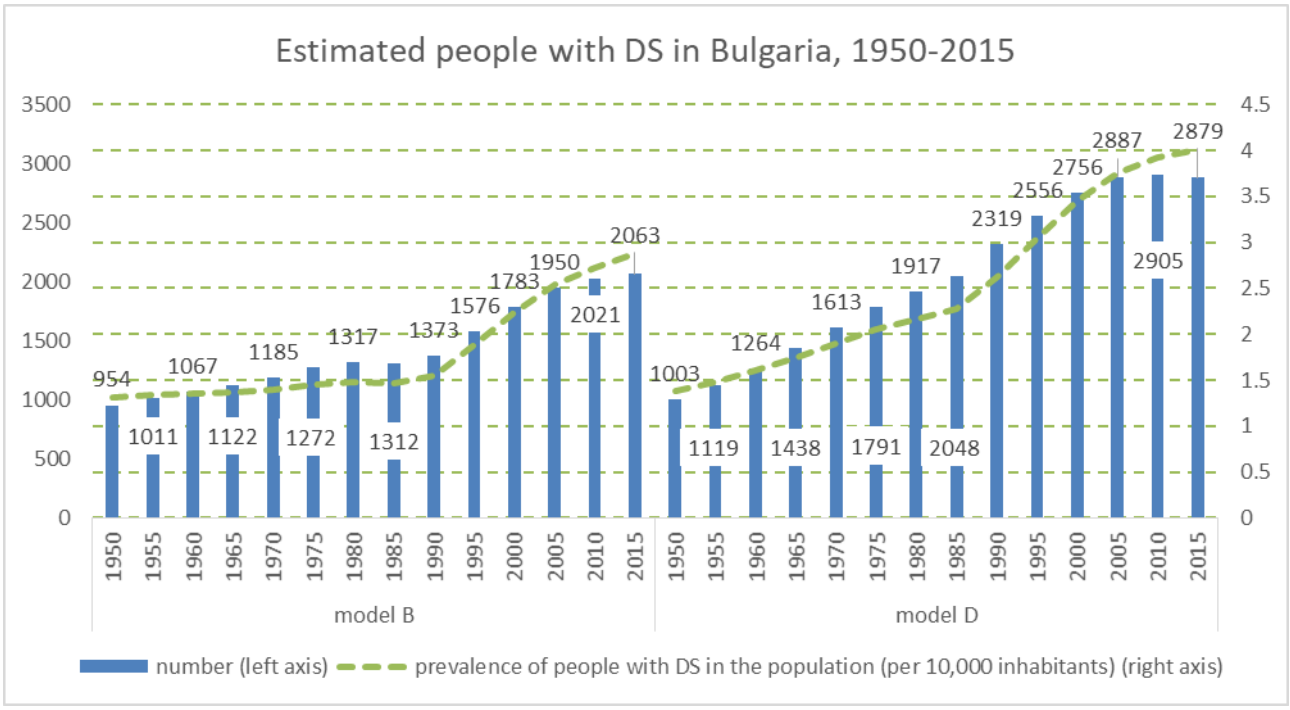

Estimates of LB prevalence for DS in Bulgaria
LB prevalence for DS per 10,000 LBs
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)

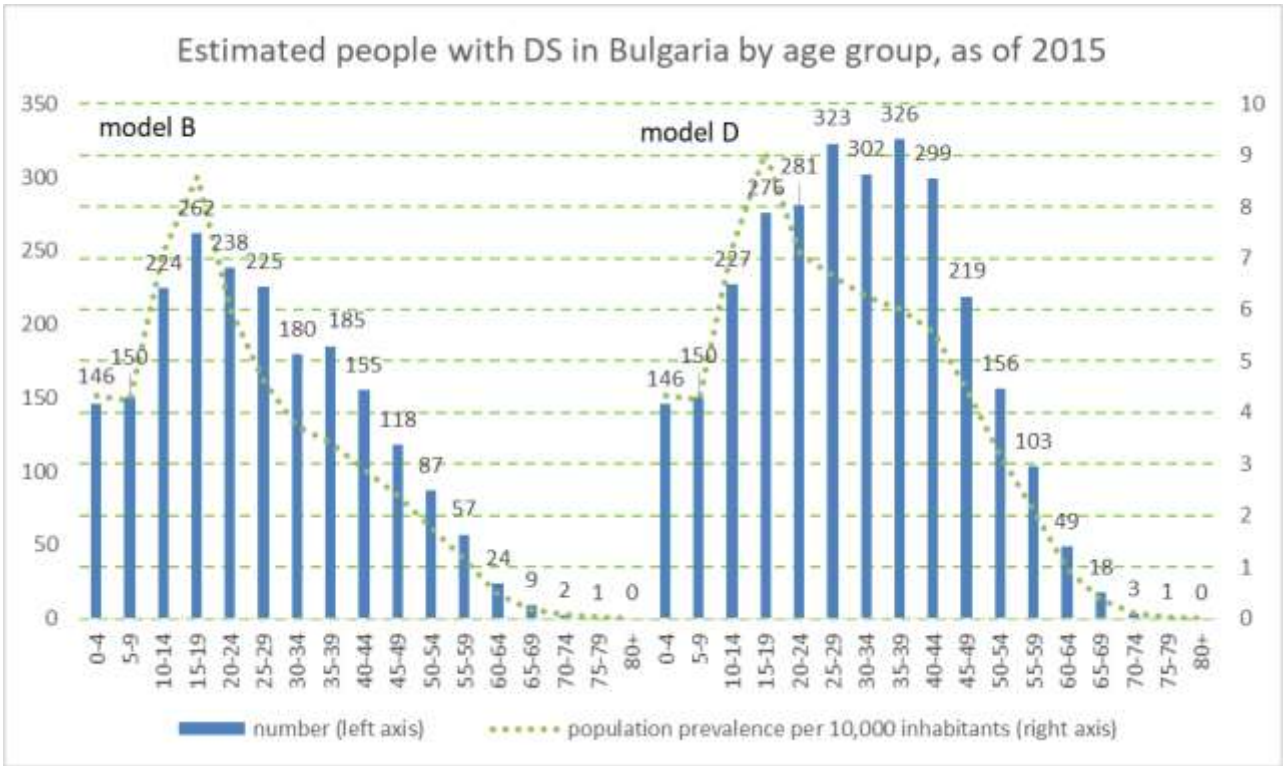

Estimated reduction in LBs with DS as a result of elective terminations in Bulgaria
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

Model A projects 4,002 people with DS alive in 2015, which corresponds to a population prevalence of 5.6 people with DS per 10,000 inhabitants. Model C projects 3,594 (5.0 per 10,000). However, both these models are unlikely, as their projections don't fit the data on age distribution of deaths with DS (see S5C). Model B and Model D are depicted in the graphs. For Bulgaria, Model B seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics (see S5C).

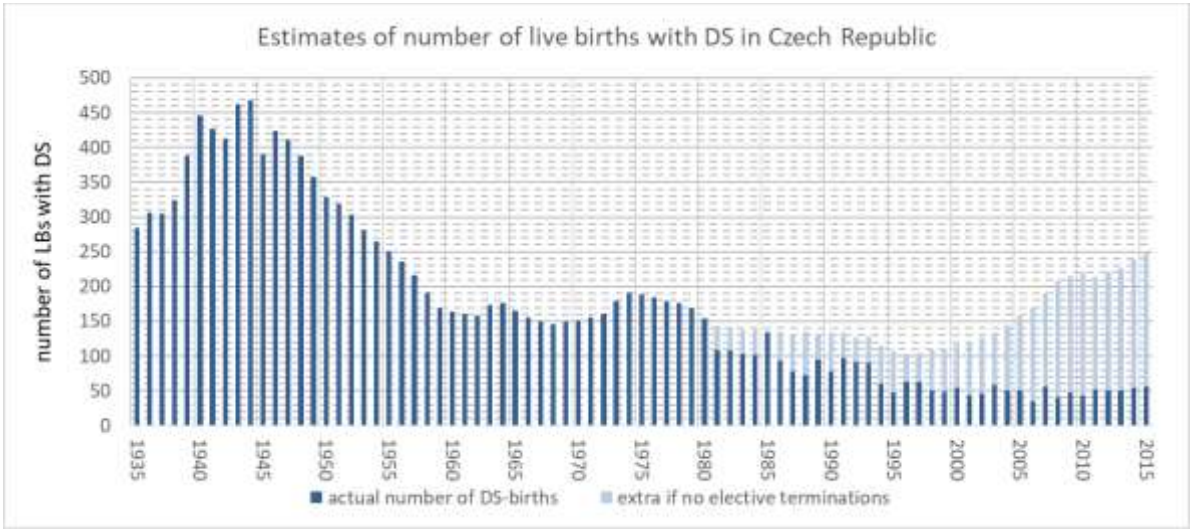


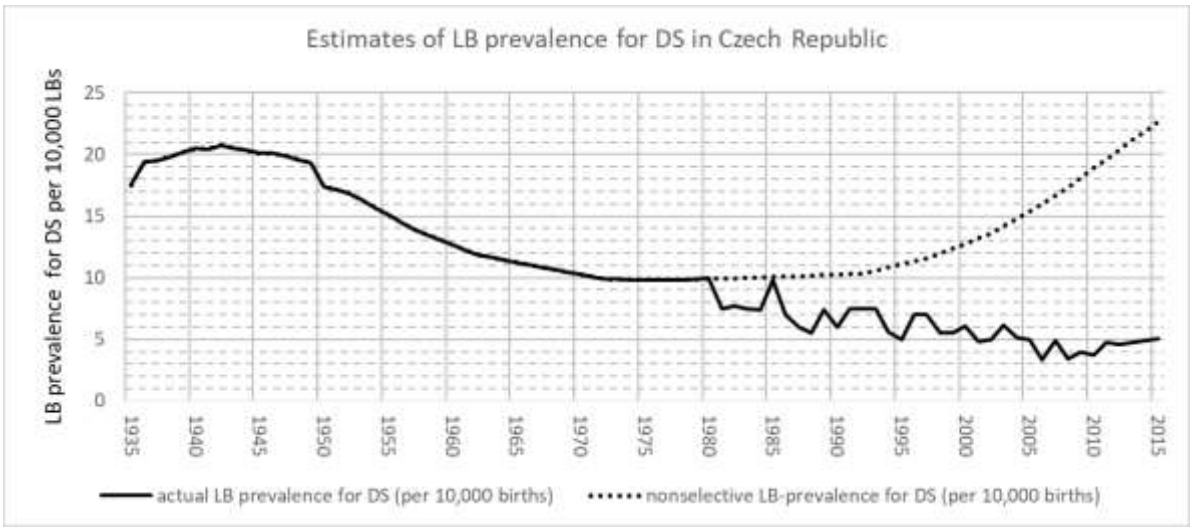


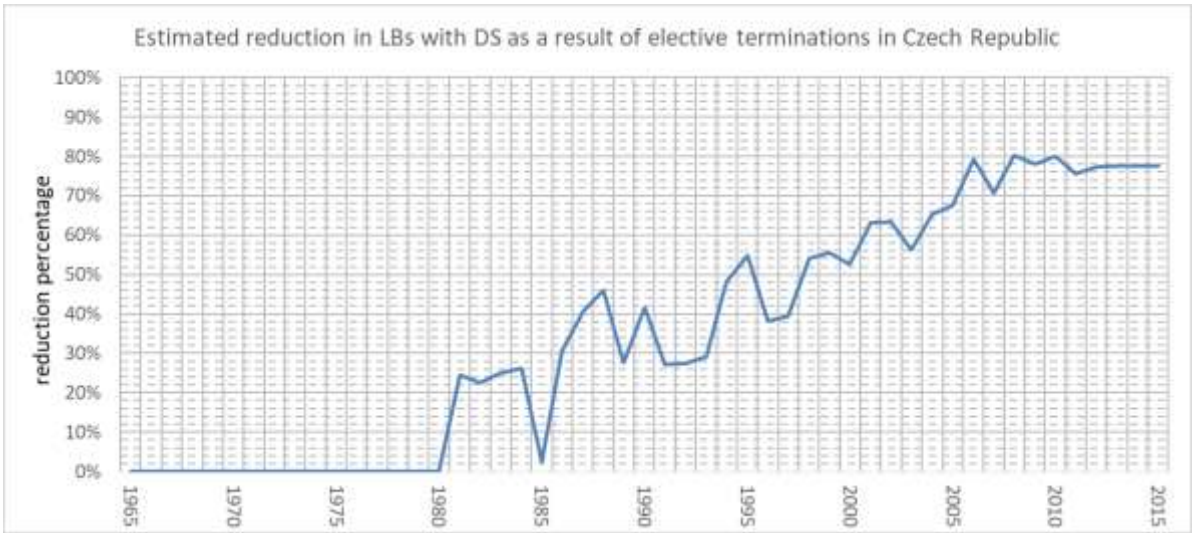

Estimated people with DS in Bulgaria, 1950-2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Bulgaria by age group, as of 2015
model B
model D
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

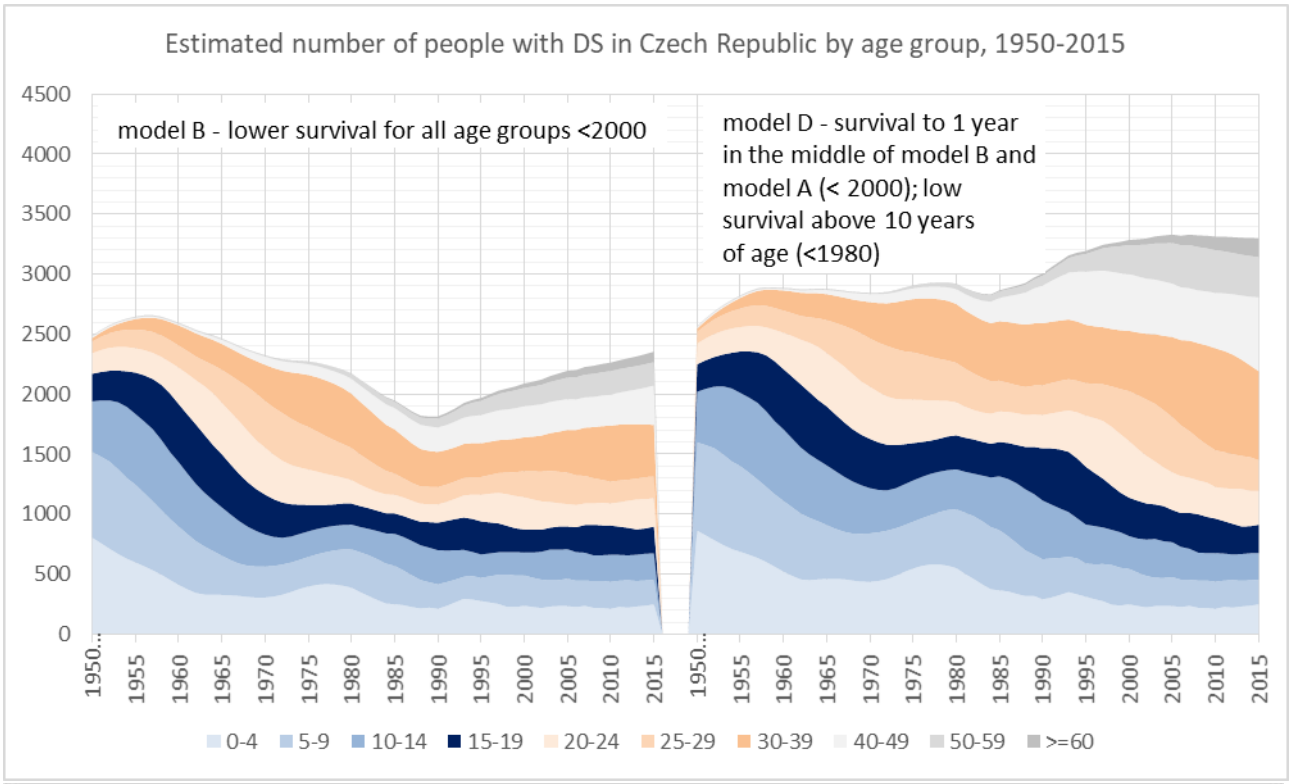
Czech Republic

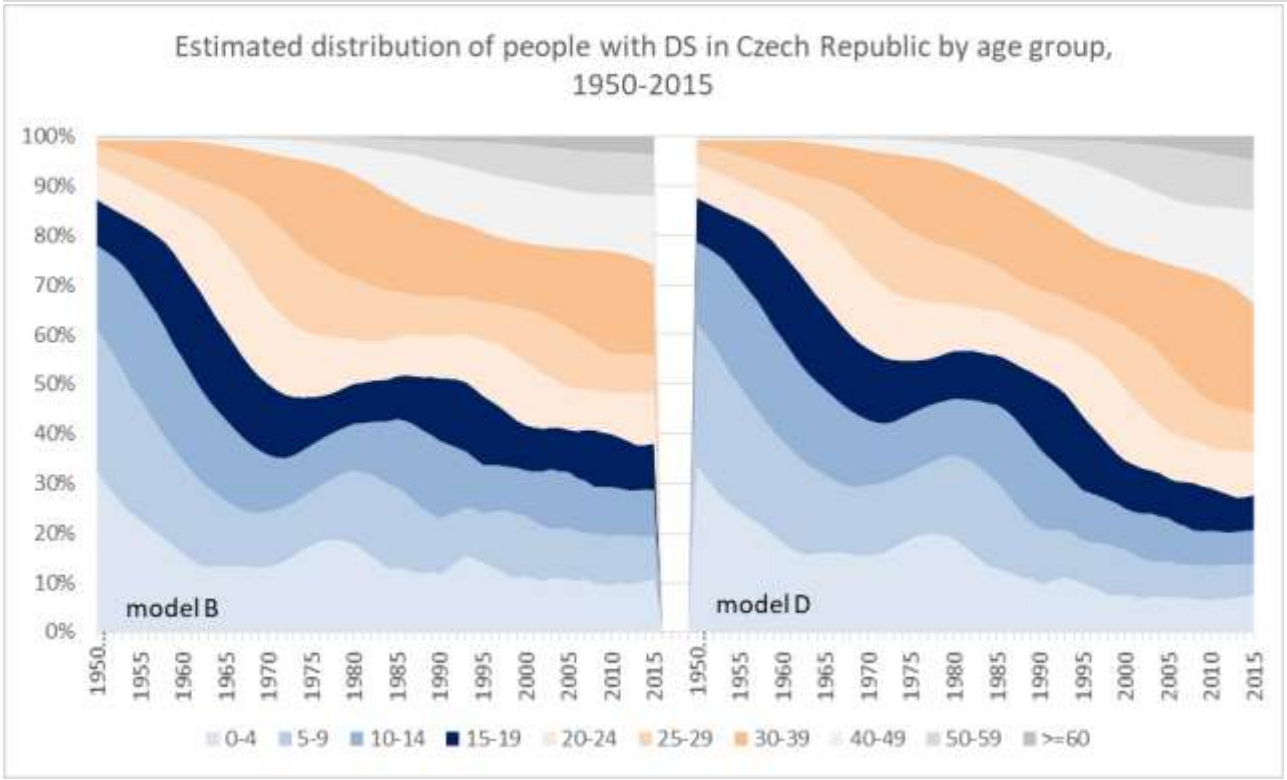


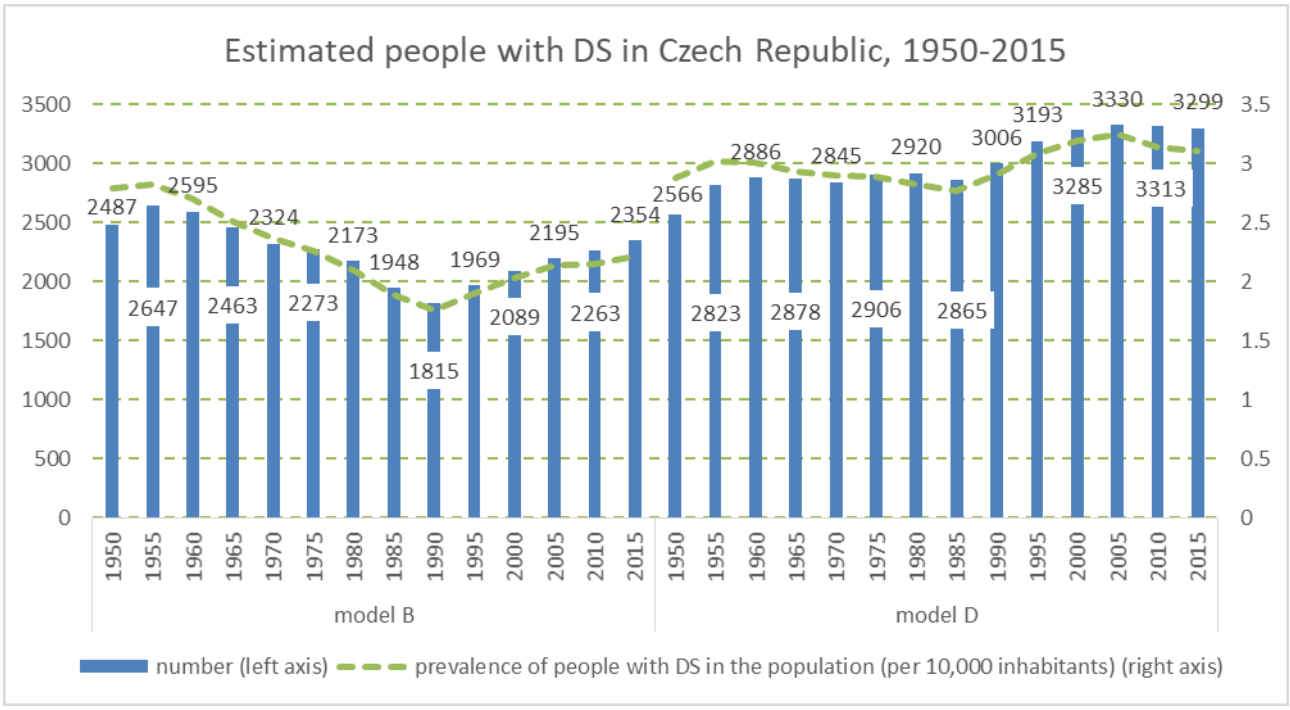


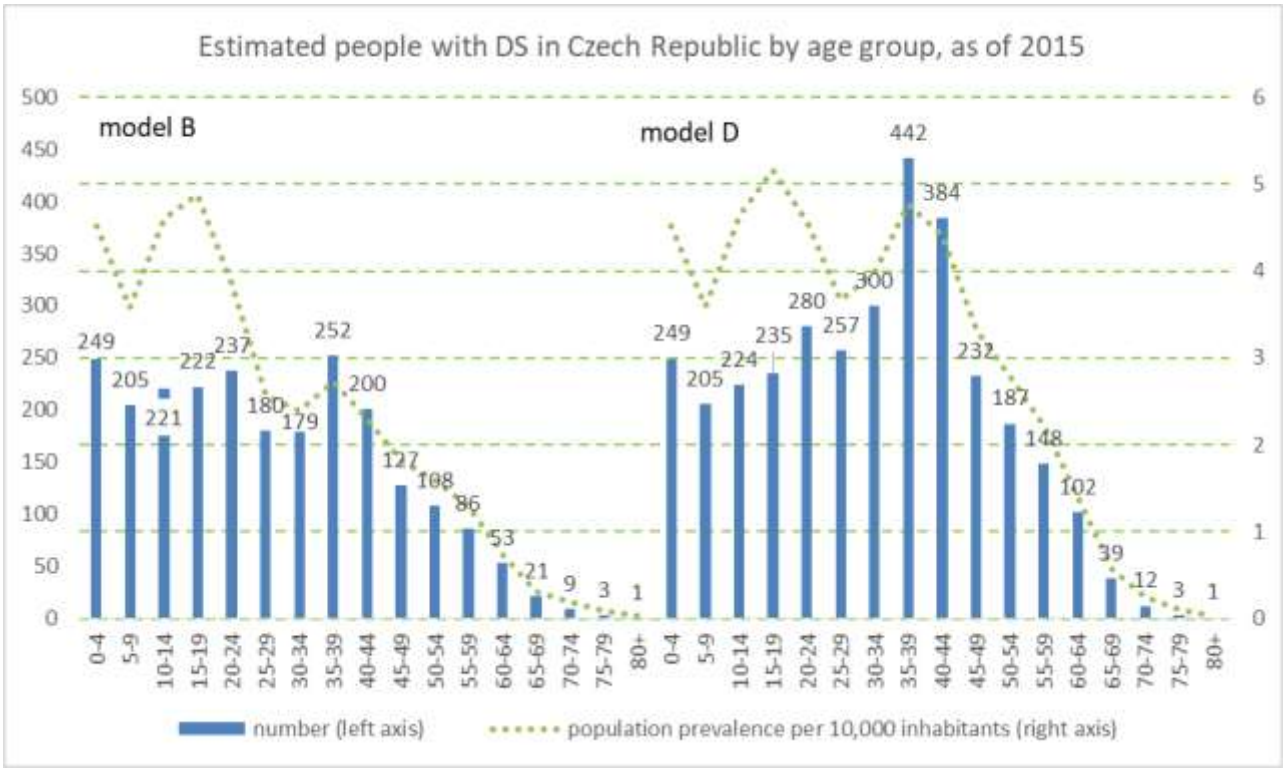


Model A projects 4,711 people with DS alive in 2015, which corresponds to a population prevalence of 4.4 people with DS per 10,000 inhabitants However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 4,092 (3.9 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Czech Republic, Model D seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics for 2005–2015, but Model B seems to be a better fit for 1994–2004 (see S5C).

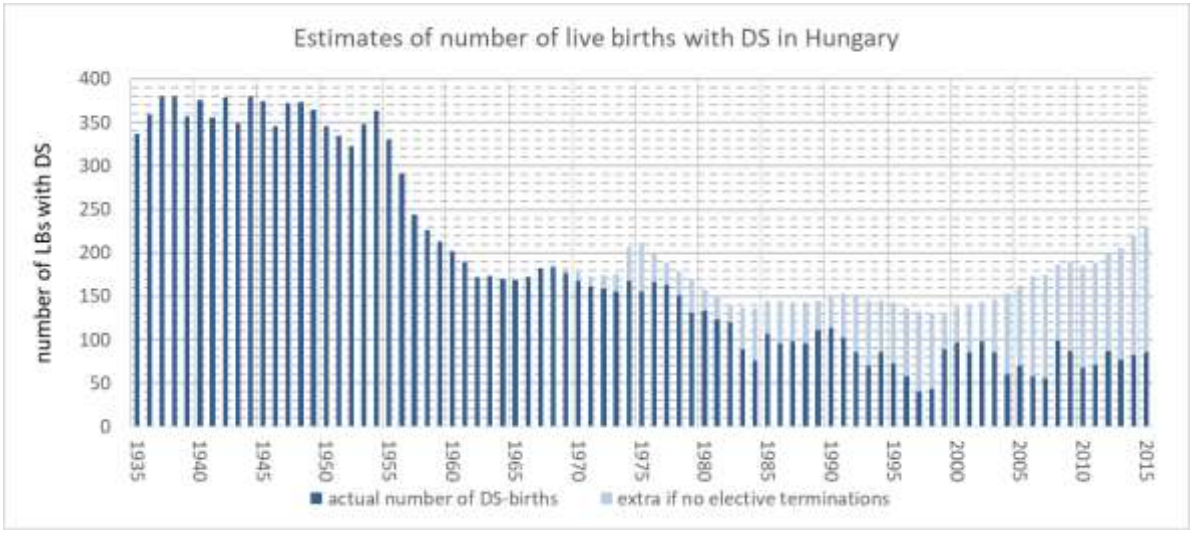


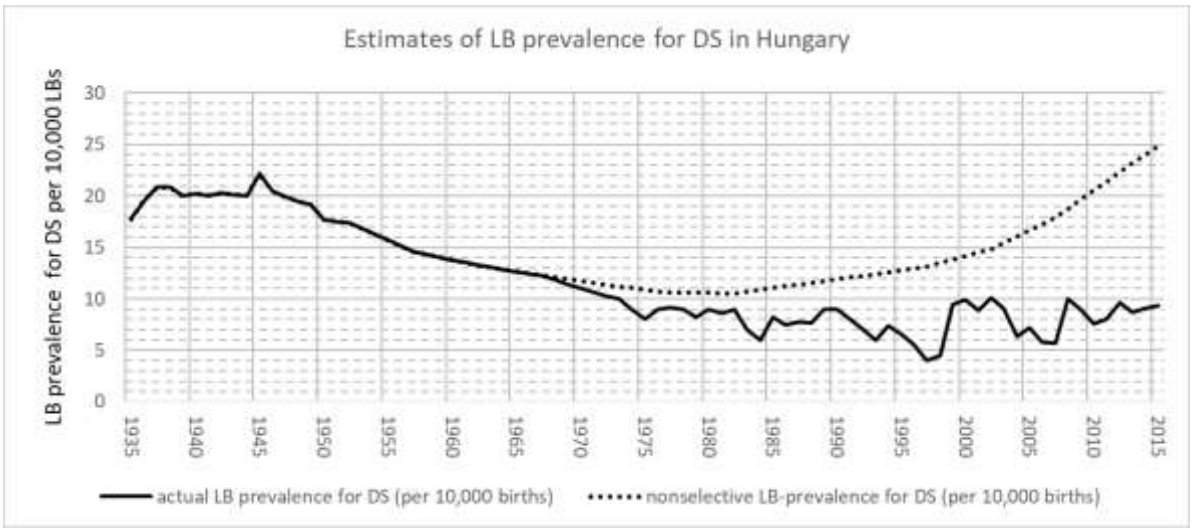


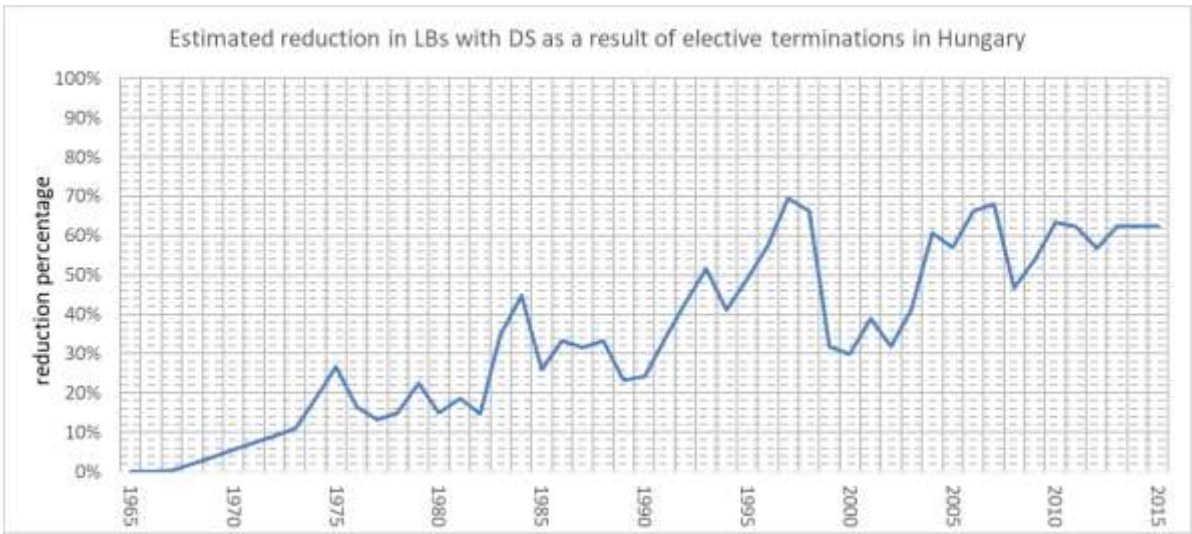

Estimated people with DS in Czech Republic, 1950-2015
3500
3000
2500
2000
1500
1000
500
0
3.5
3
2.5
2
1.5
1
0.5
0
2487
2647
2595
2463
2324
2273
2173
1948
1815
1969
2089
2195
2263
2354
2566
2823
2886
2878
2845
2906
2920
2865
3006
3193
3285
3330
3313
3299
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Czech Republic by age group, as of 2015
model B
model D
500
450
400
350
300
250
200
150
100
50
0
6
5
4
3
2
1
0
249
205
221
222
237
180
179
252
200
127
108
86
53
21
9
3
1
249
205
224
235
280
257
300
442
384
232
187
148
102
39
12
3
1
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

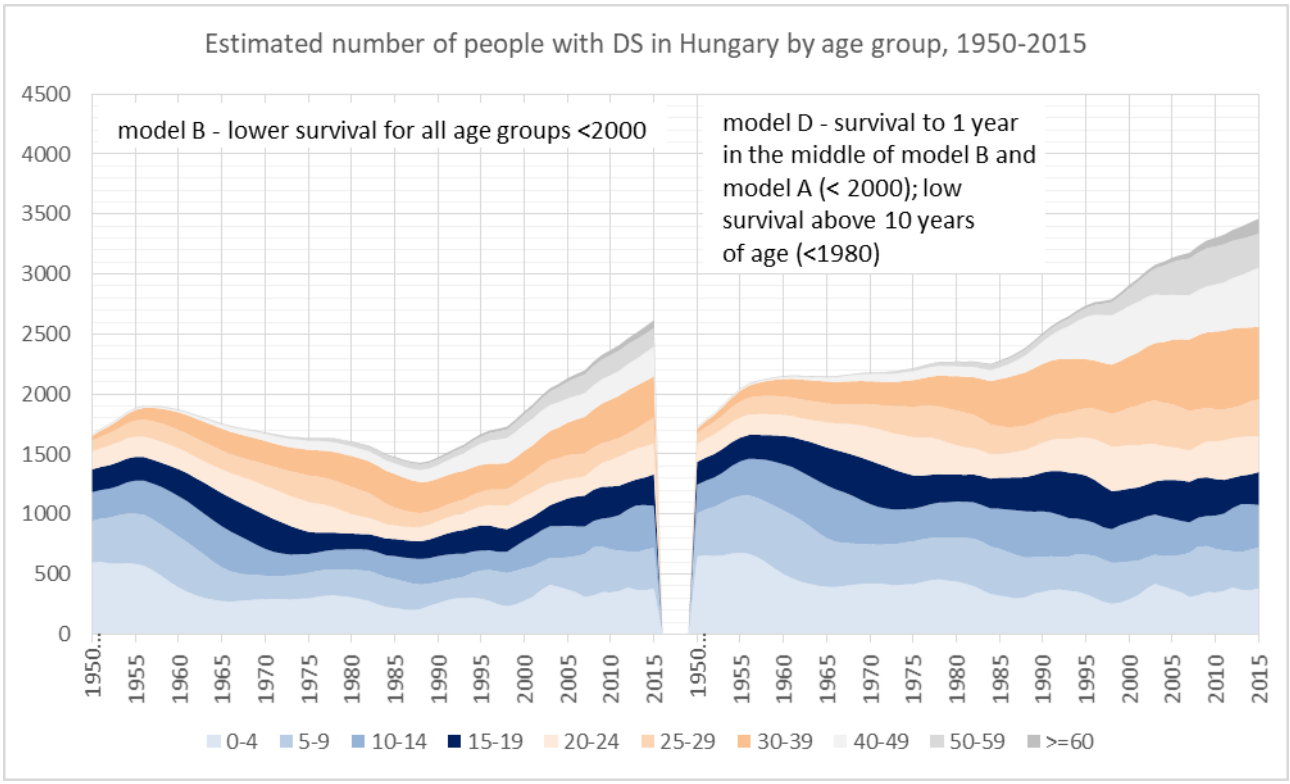
Hungary

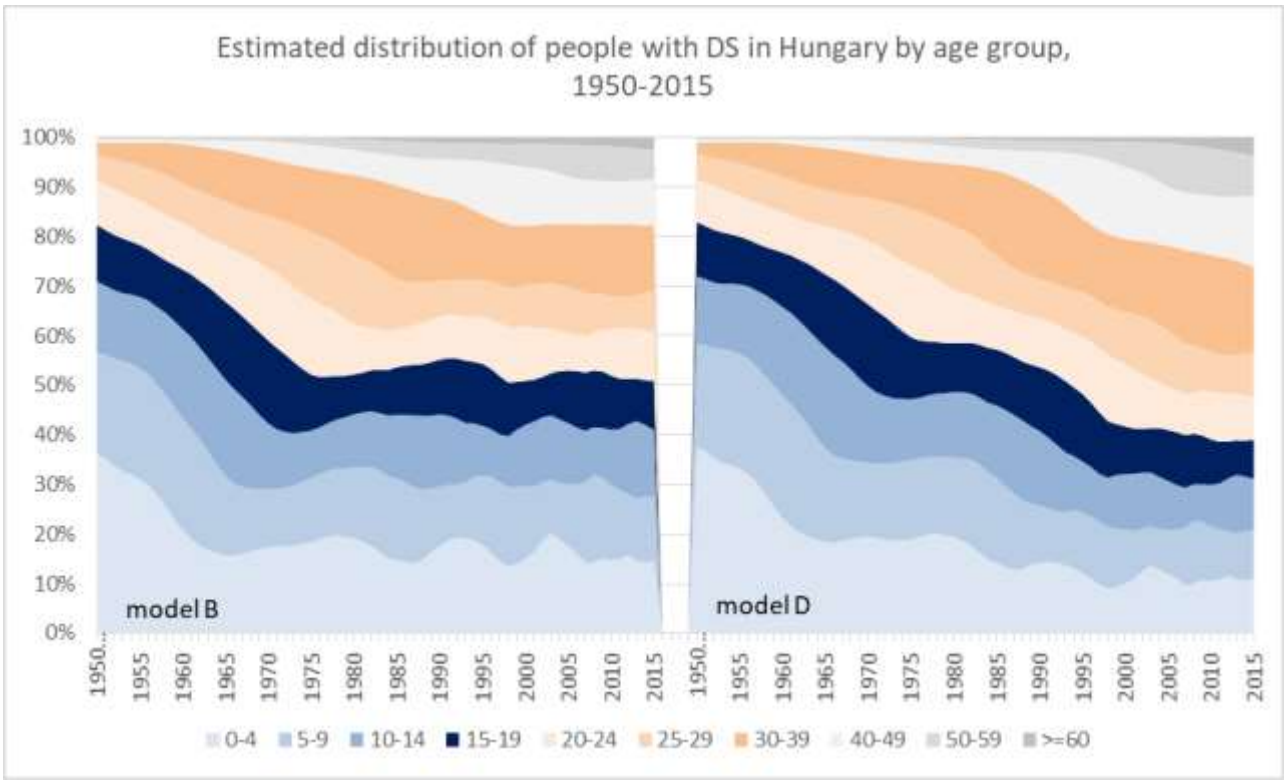

Estimates of number of live births with DS in Hungary
number of LBs with DS
400
350
300
250
200
150
100
50
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

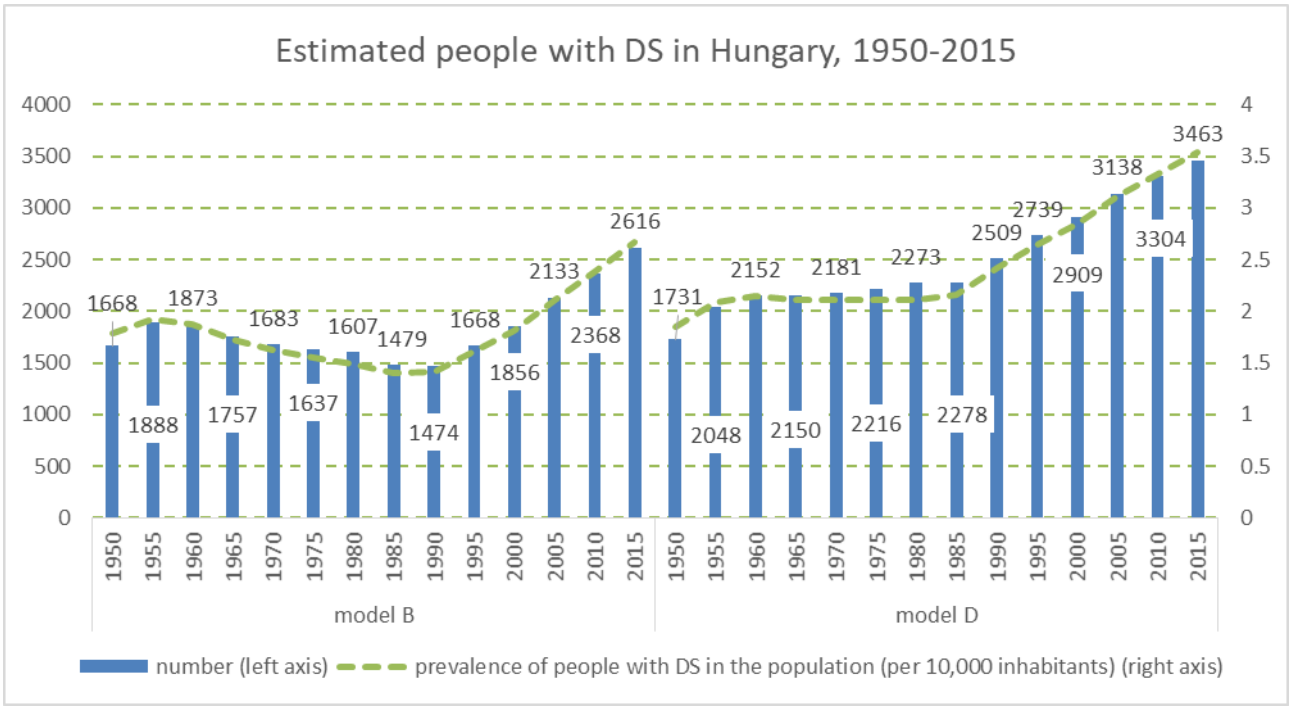

Estimates of LB prevalence for DS in Hungary
LB prevalence for DS per 10,000 LBs
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)

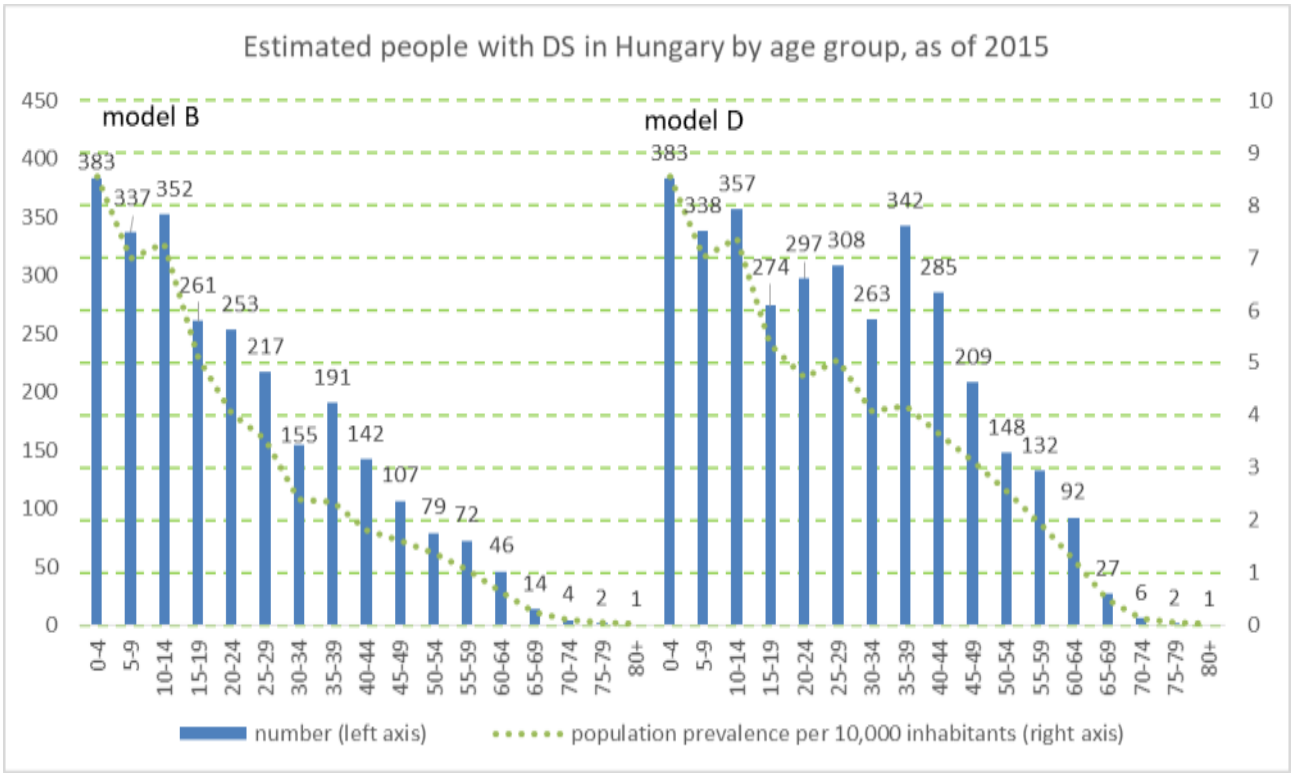

Estimated reduction in LBs with DS as a result of elective terminations in Hungary
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

Model A projects 4,689 people with DS alive in 2015, which corresponds to a population prevalence of 4.8 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 4,193 (4.3 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Hungary, Model D seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics for 2005–2015, but Model B seems to be a better fit for 1996–2006 (see S5C).

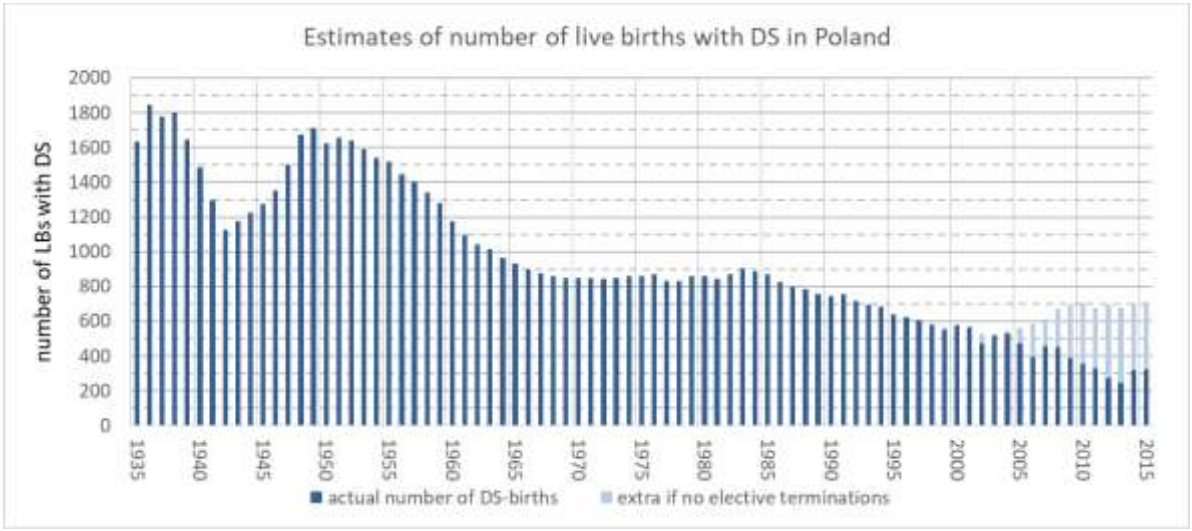


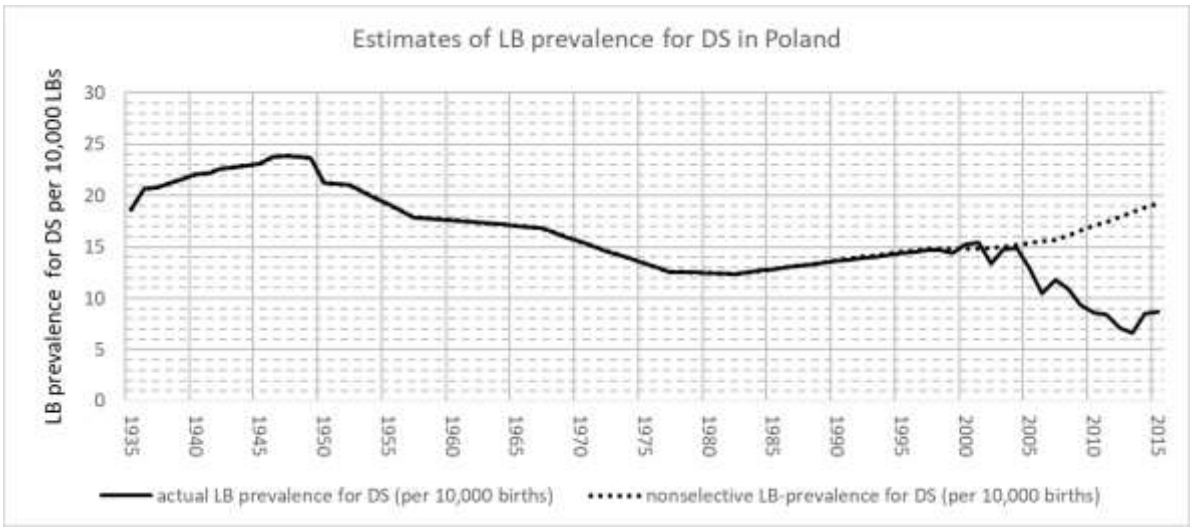


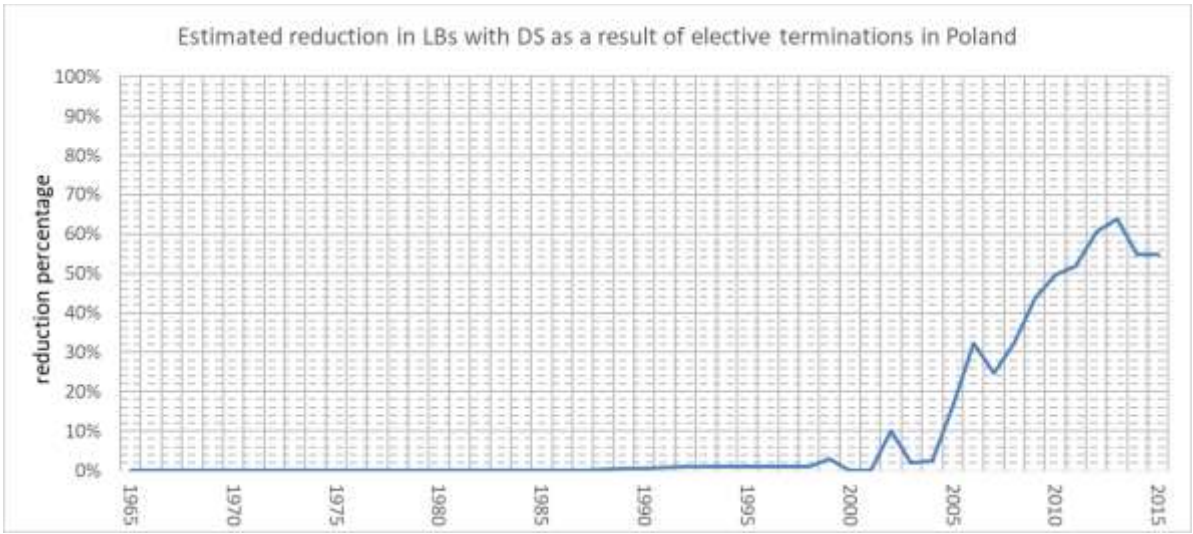

Estimated people with DS in Hungary, 1950-2015
4000
3500
3000
2500
2000
1500
1000
500
0
4
3.5
3
2.5
2
1.5
1
0.5
0
1668
1888
1873
1757
1683
1637
1607
1479
1474
1668
1856
2133
2368
2616
1731
2048
2152
2150
2181
2216
2273
2278
2509
2739
2909
3138
3304
3463
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Hungary by age group, as of 2015
model B
model D
450
400
350
300
250
200
150
100
50
0
10
9
8
7
6
5
4
3
2
1
0
383
337
352
261
253
217
155
191
142
107
79
72
46
14
4
2
1
383
338
357
274
297
308
263
342
285
209
148
132
92
27
6
2
1
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

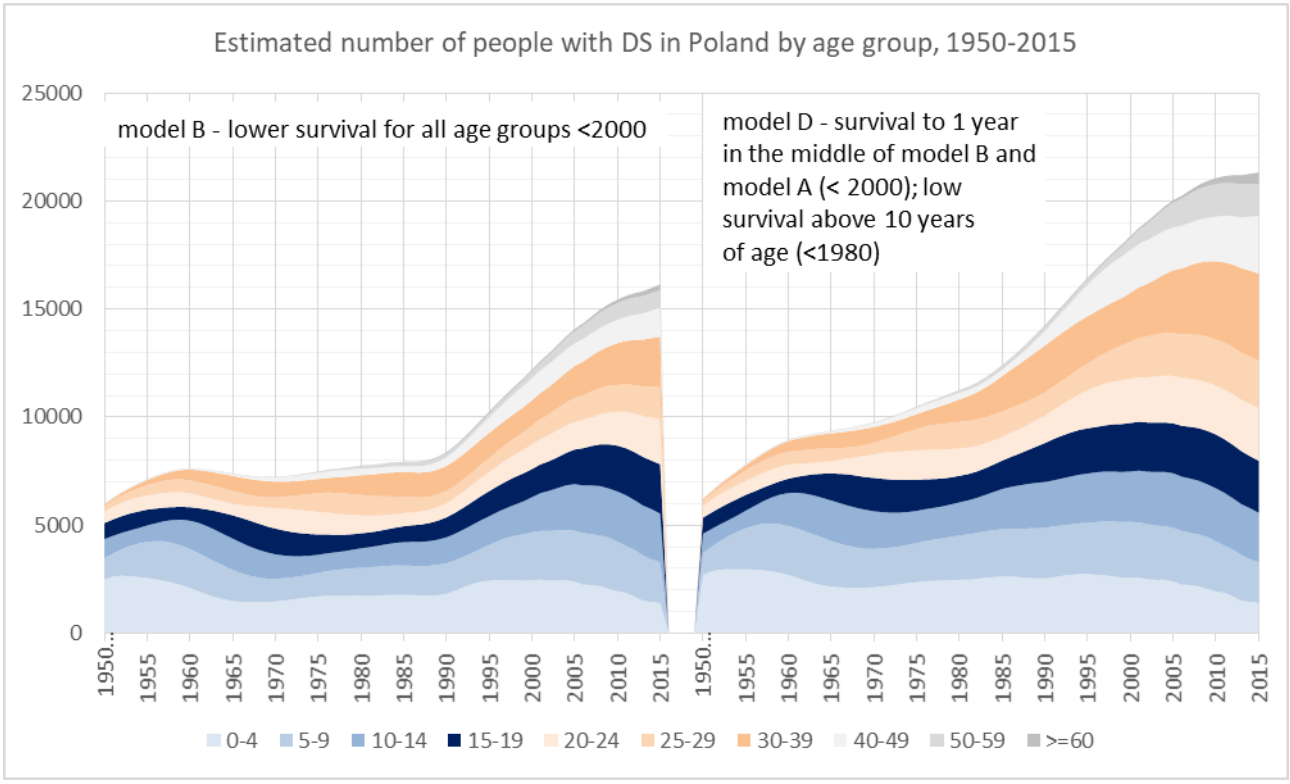
Poland

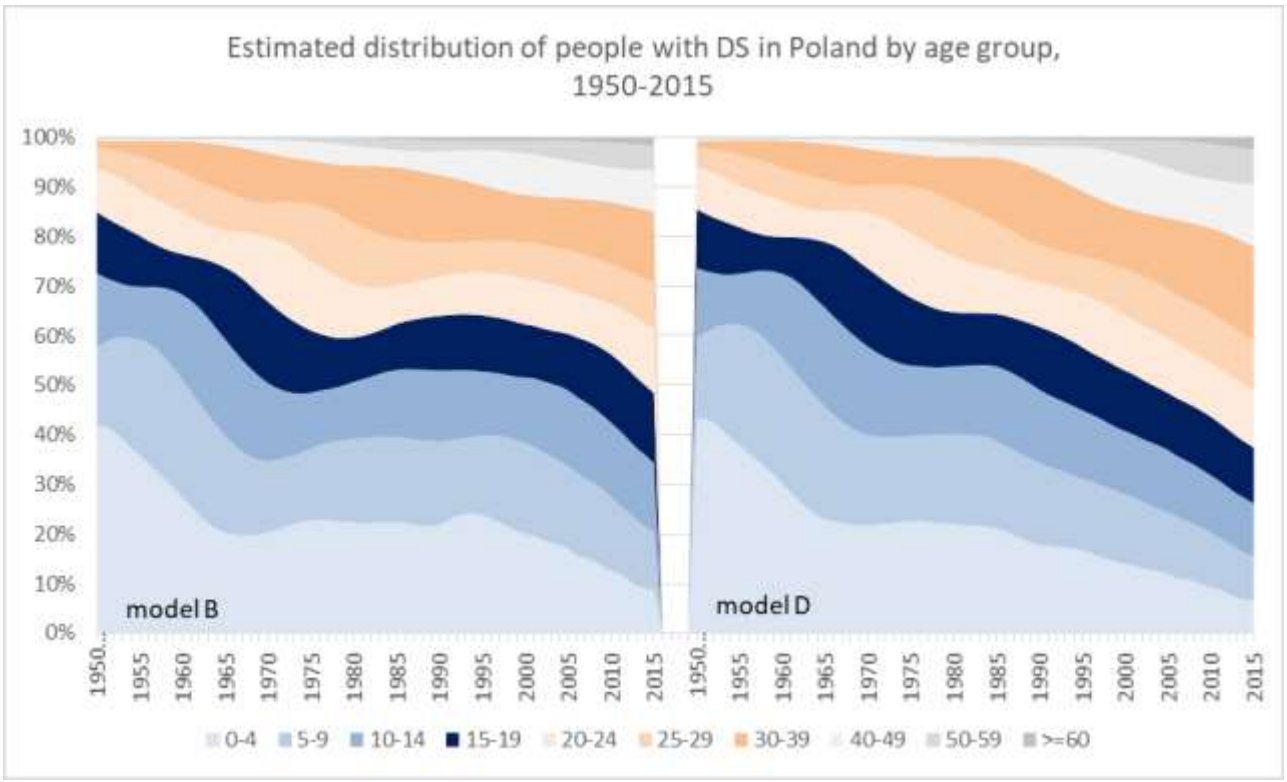

Estimates of number of live births with DS in Poland
number of LBs with DS
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

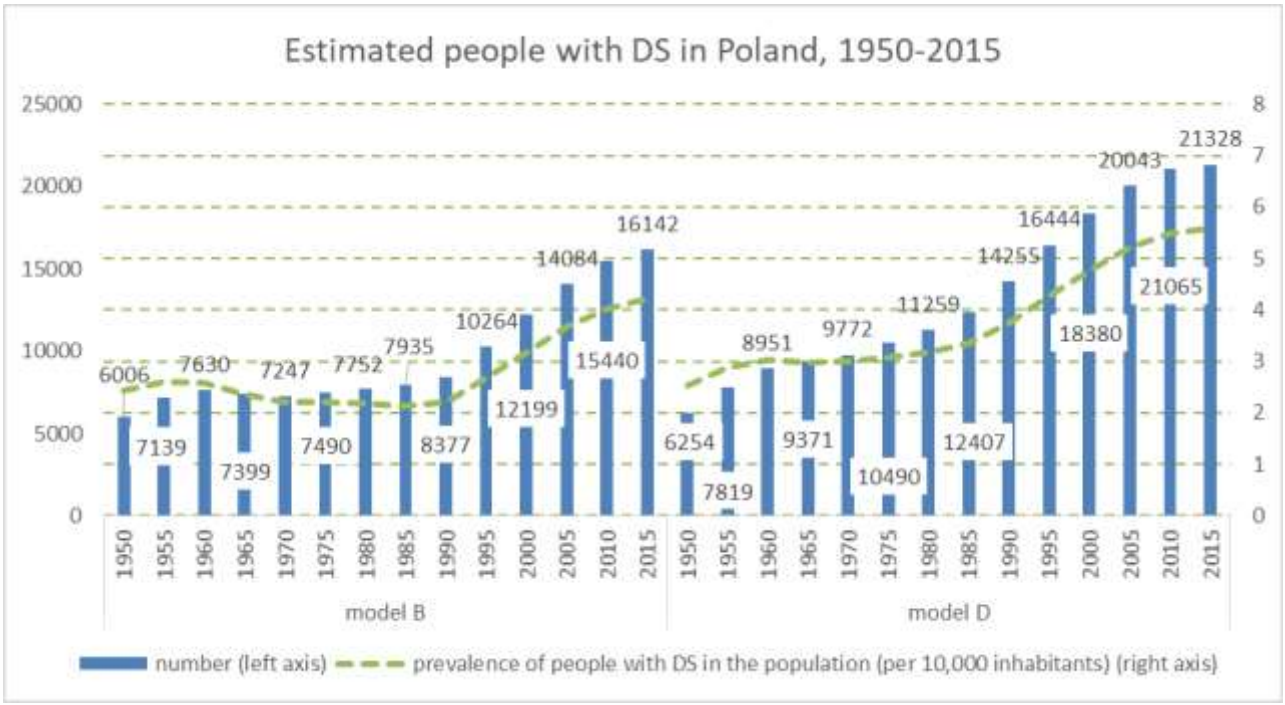

Estimates of LB prevalence for DS in Poland
LB prevalence for DS per 10,000 LBs
30
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)

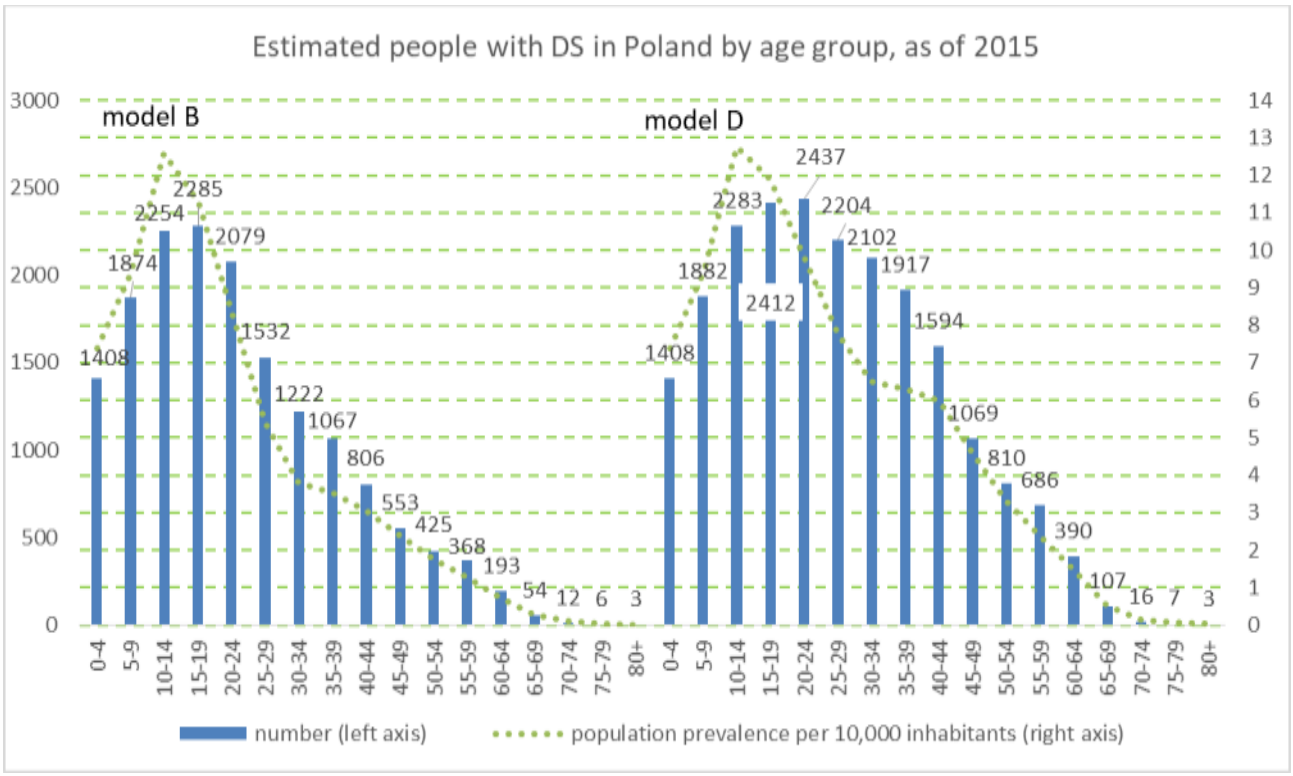

Estimated reduction in LBs with DS as a result of elective terminations in Poland
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

Model A projects 28,219 people with DS alive in 2015, which corresponds to a population prevalence of 7.4 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 25,925 (6.8 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Poland, Model D seems to have a better fit with the age distribution of deaths with DS as reported in the national (see S5C).

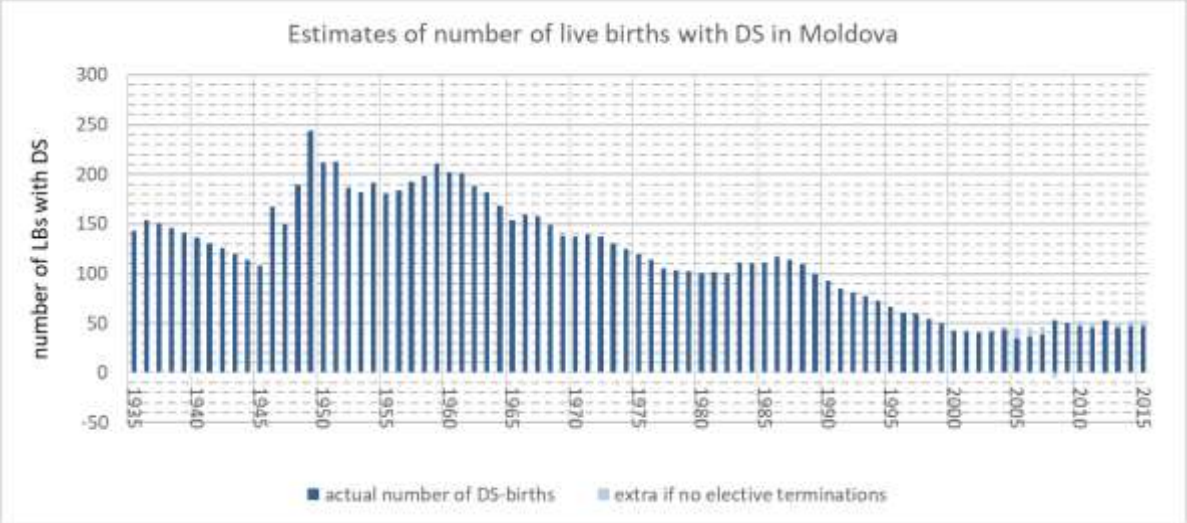


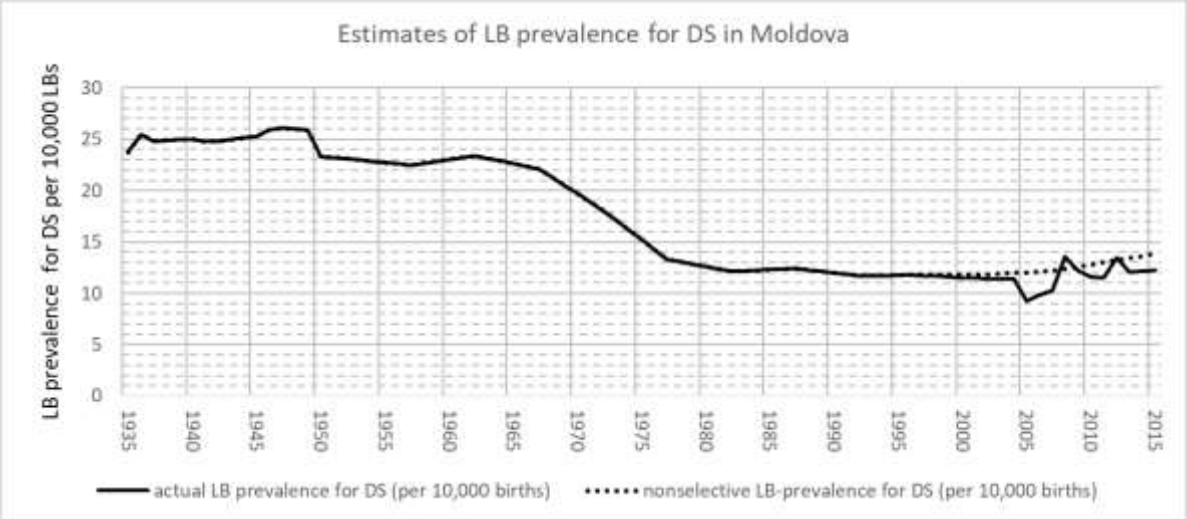


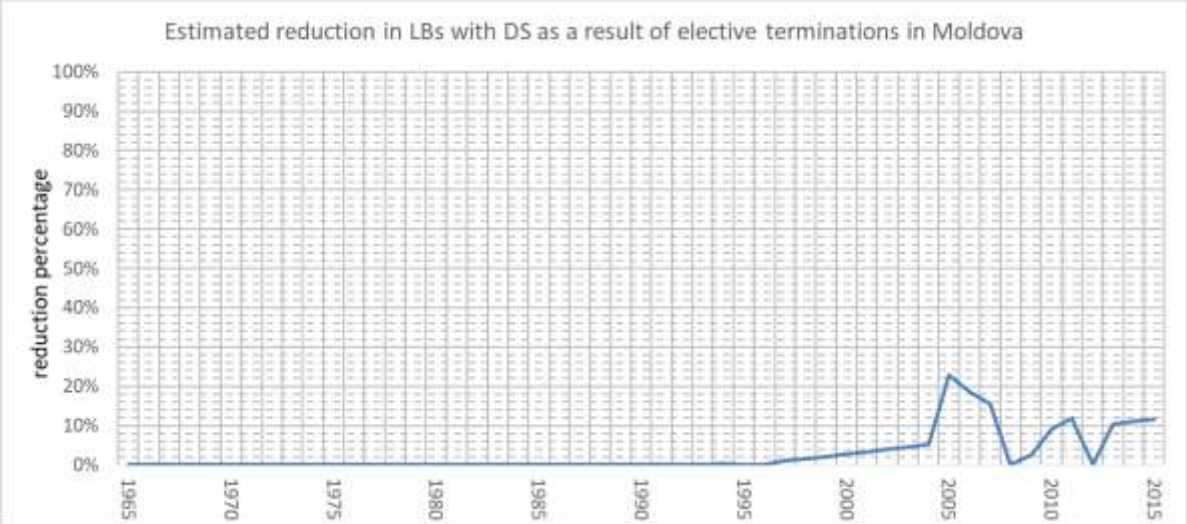

Estimated people with DS in Poland, 1950-2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Poland by age group, as of 2015
model B
model D
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Republic of Moldova

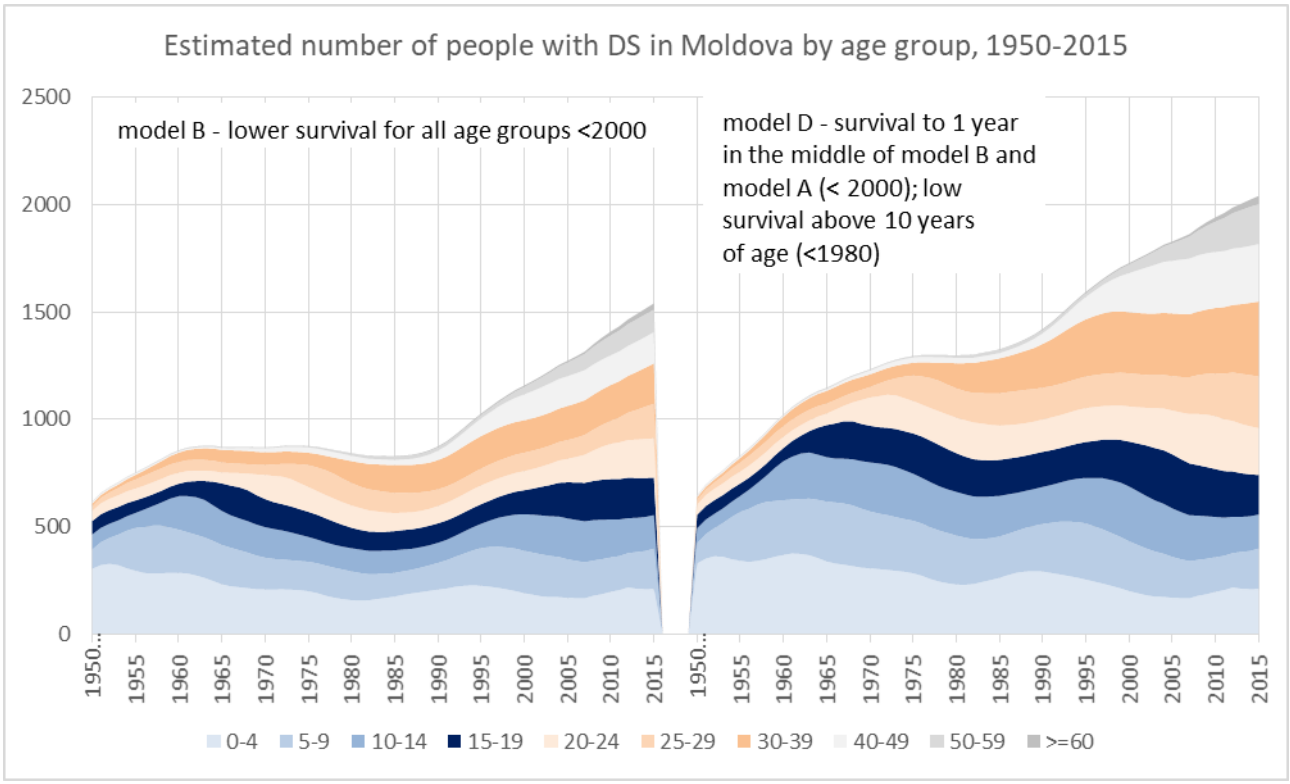


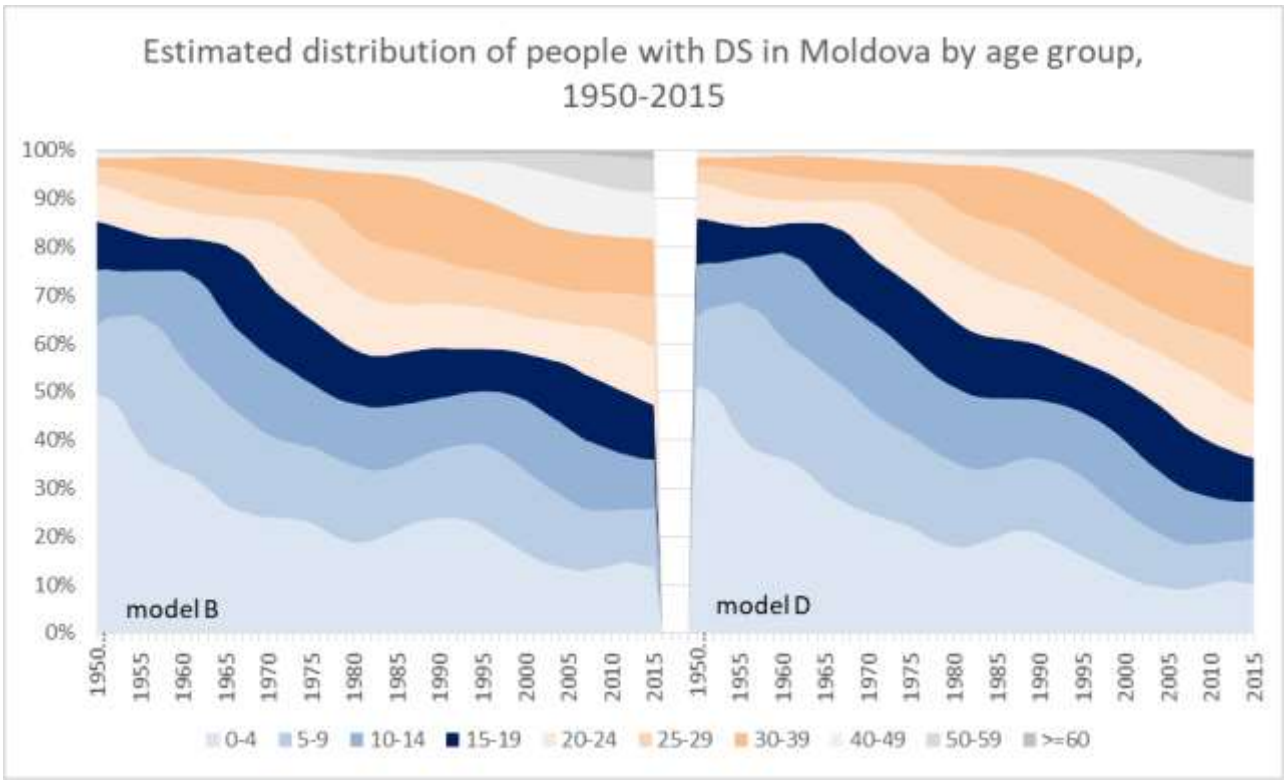


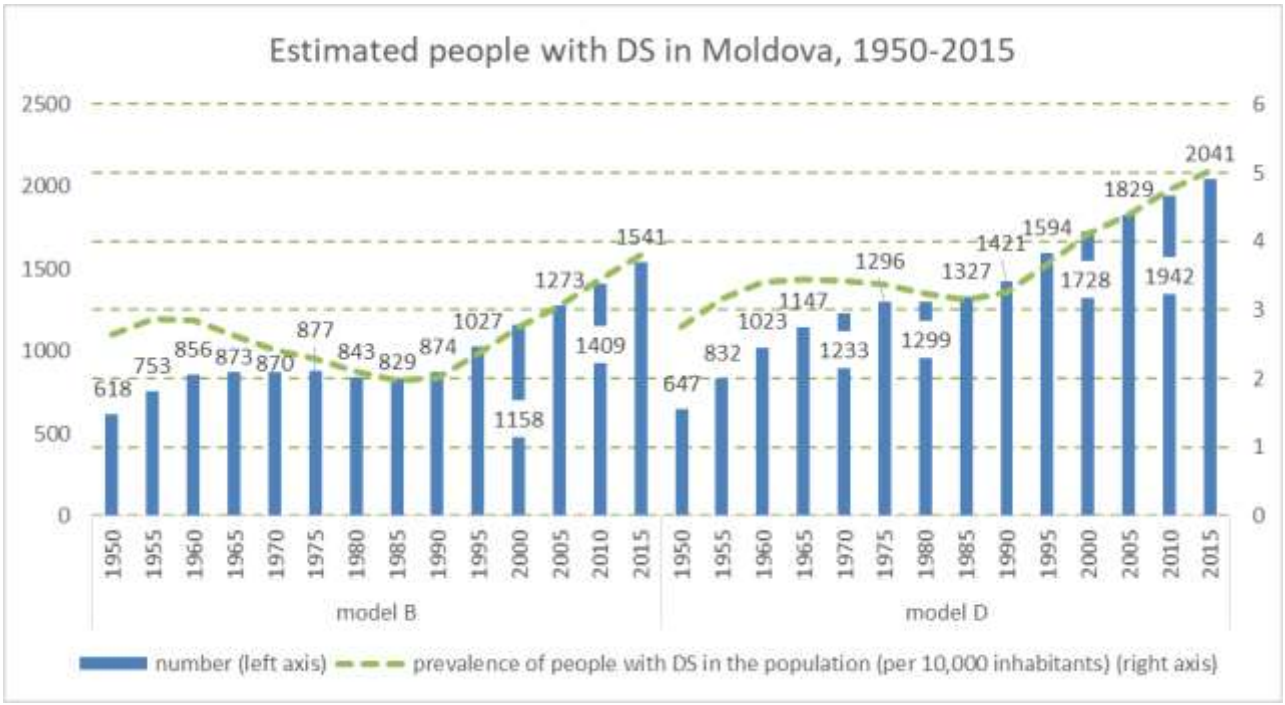


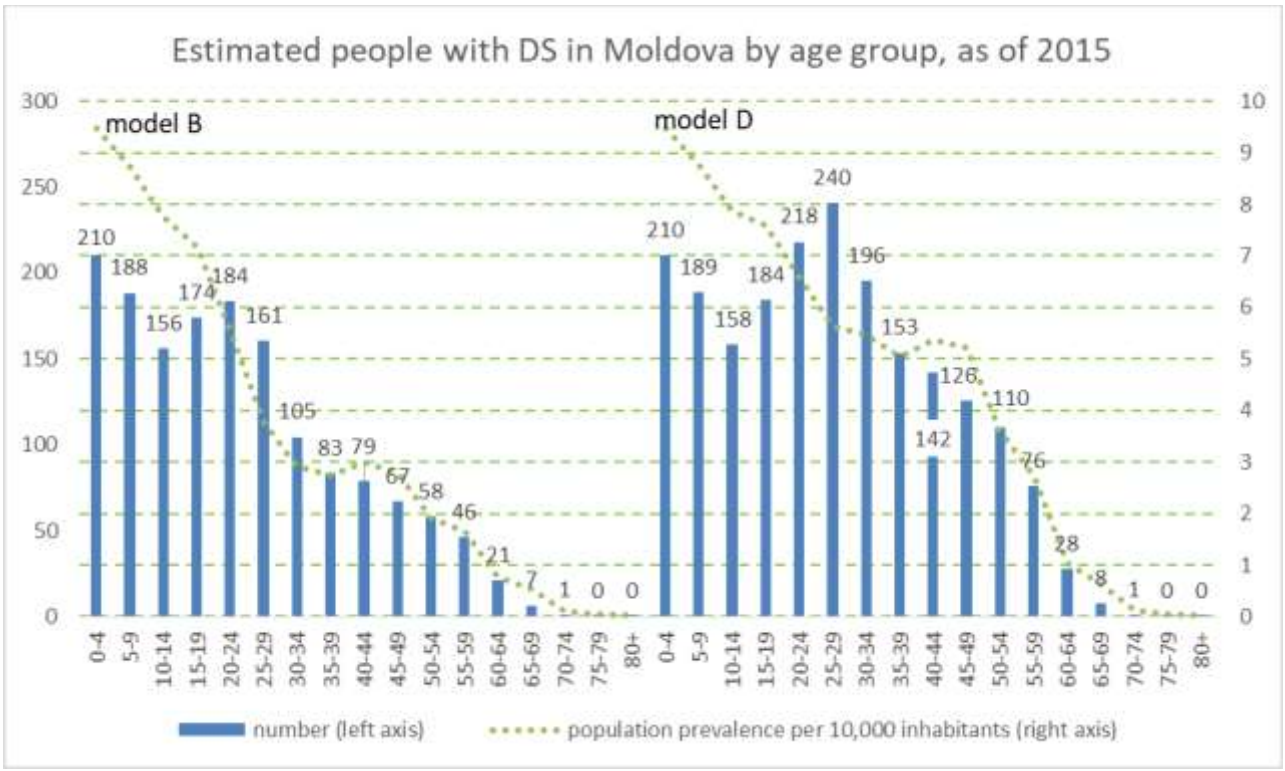
In the graph, negative reduction percentages (if nonselective prevalence is smaller than actual prevalence) have been set at zero.

Model A projects 2,953 people with DS alive in 2015, which corresponds to a population prevalence of 7.3 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 2,683 (6.6 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Moldova, Model B seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics for 2005–2015, but Model D seems to be a better fit for 1996–2006 (see S5C).

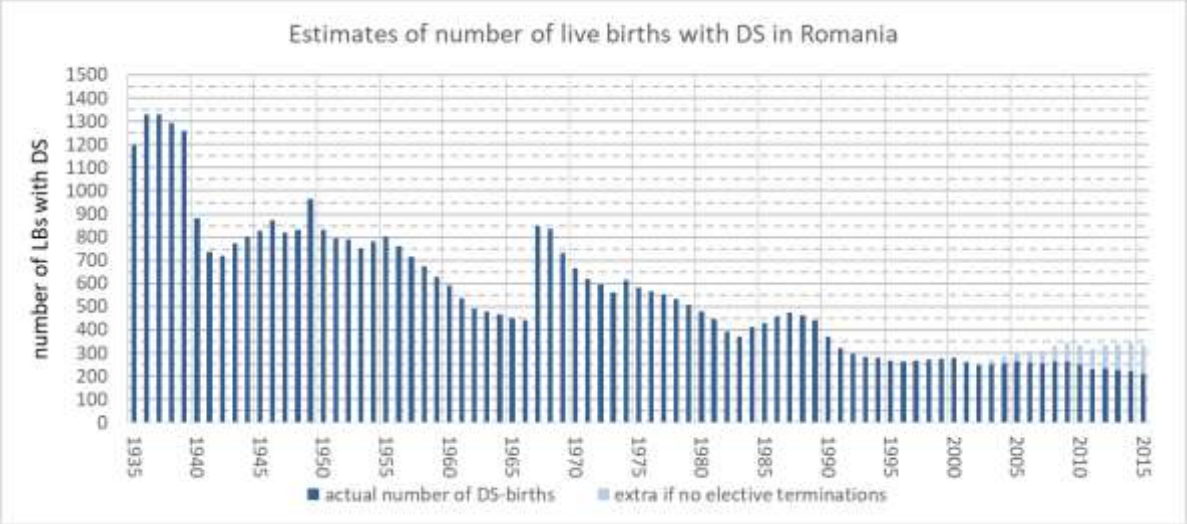


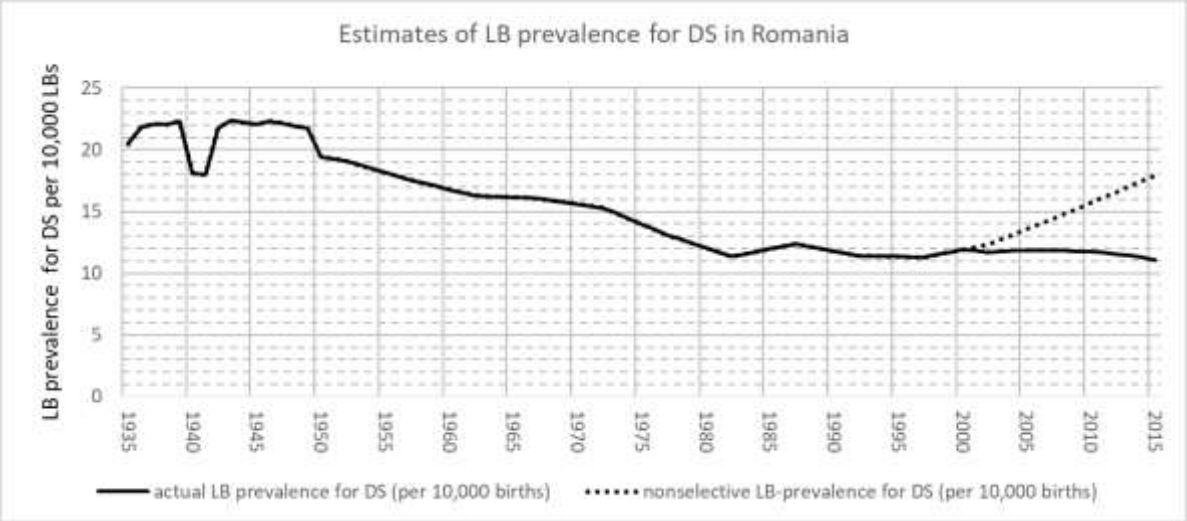


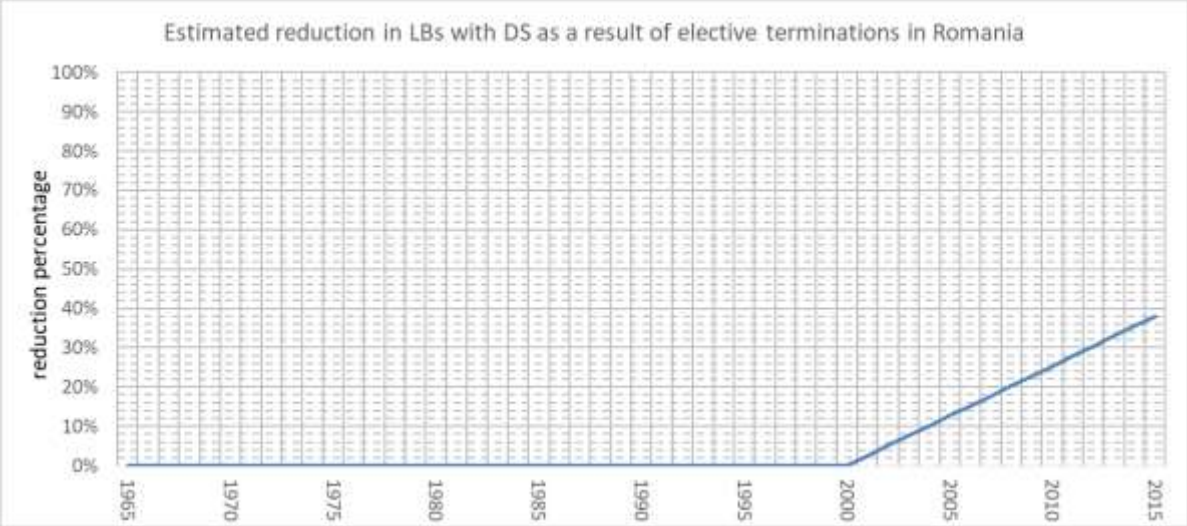

Estimated people with DS in Moldova, 1950-2015
2500
2000
1500
1000
500
0
6
5
4
3
2
1
0
618
753
856
873
870
877
843
829
874
1027
1158
1273
1409
1541
647
832
1023
1147
1233
1296
1299
1327
1421
1594
1728
1829
1942
2041
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Moldova by age group, as of 2015
300
250
200
150
100
50
0
10
9
8
7
6
5
4
3
2
1
0
model B
model D
210
188
156
174
184
161
105
83
79
67
58
46
21
7
1
0
0
210
189
158
184
218
240
196
153
126
142
110
76
28
8
1
0
0
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

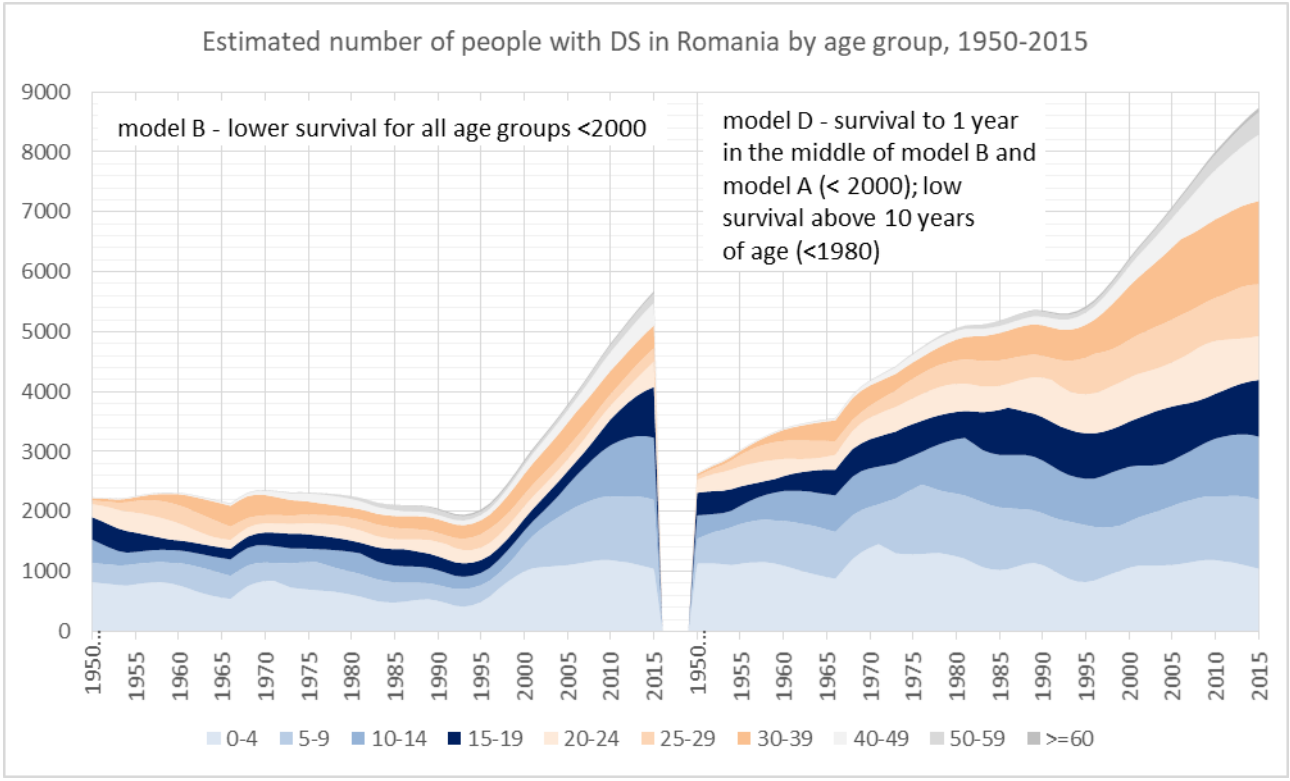
Romania

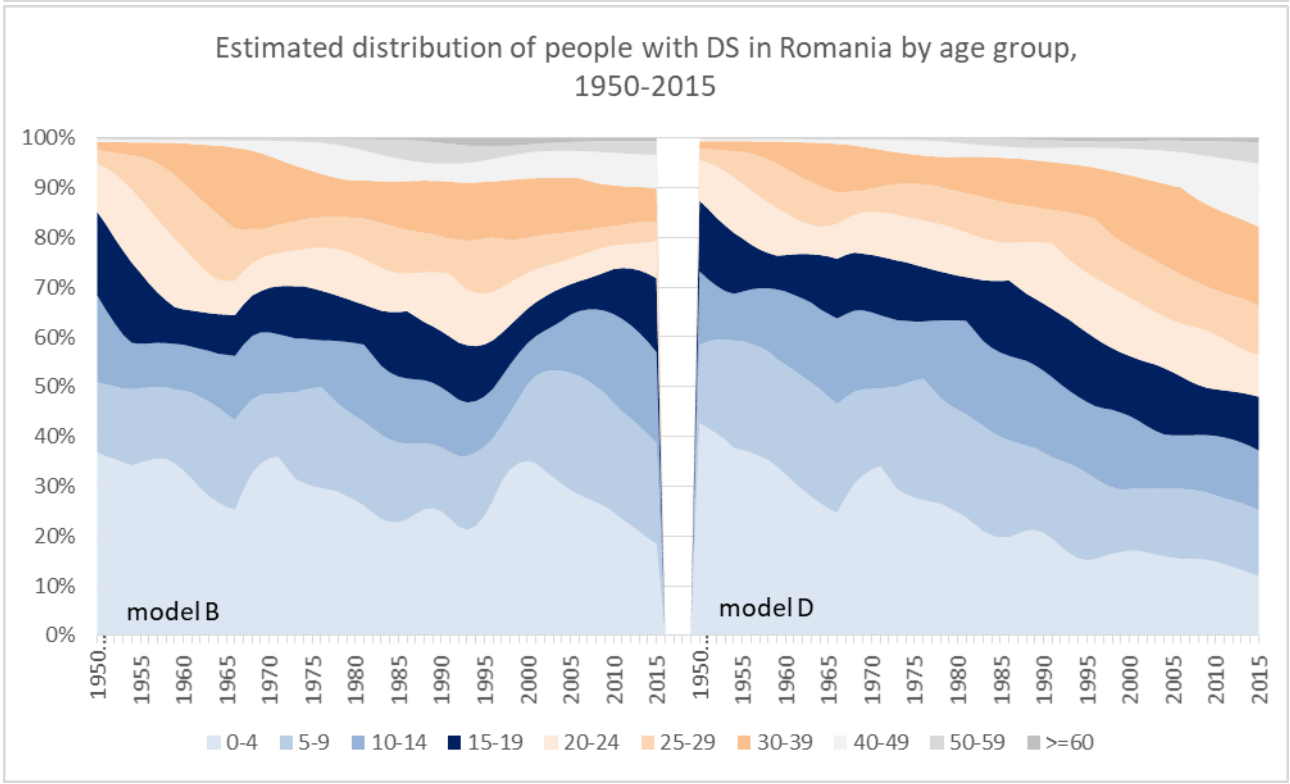

Estimates of number of live births with DS in Romania
number of LBs with DS
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

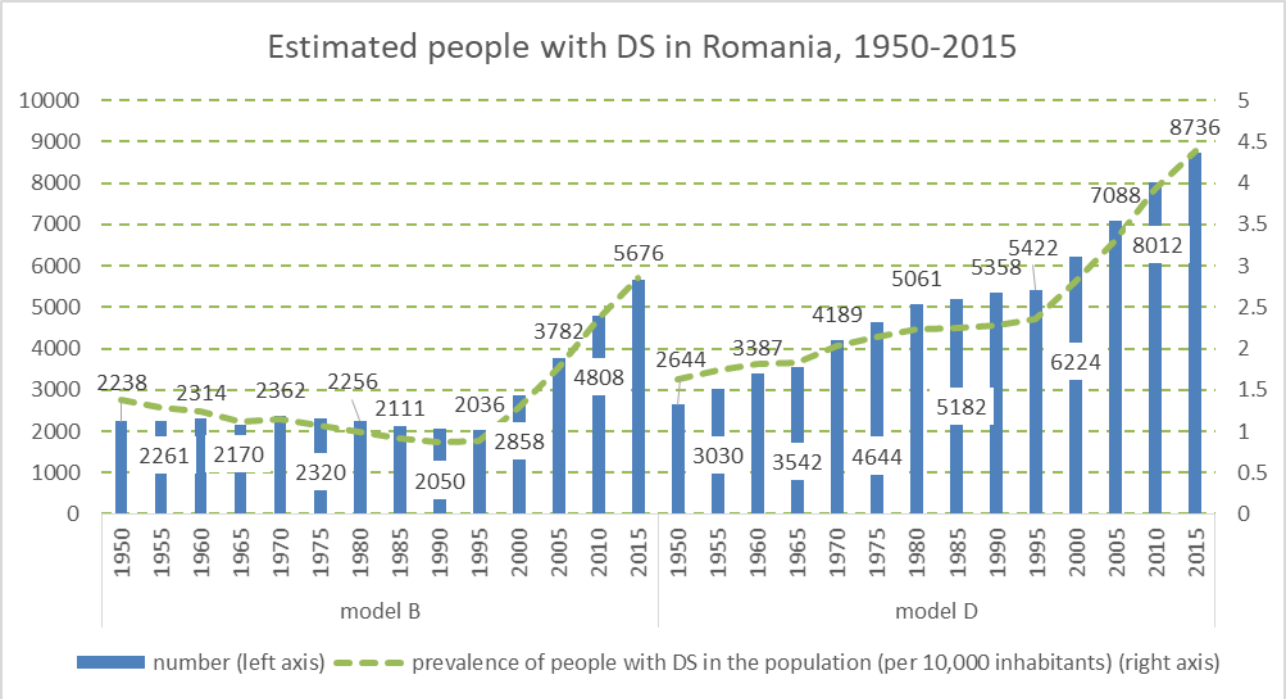

Estimates of LB prevalence for DS in Romania
LB prevalence for DS per 10,000 LBs
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)

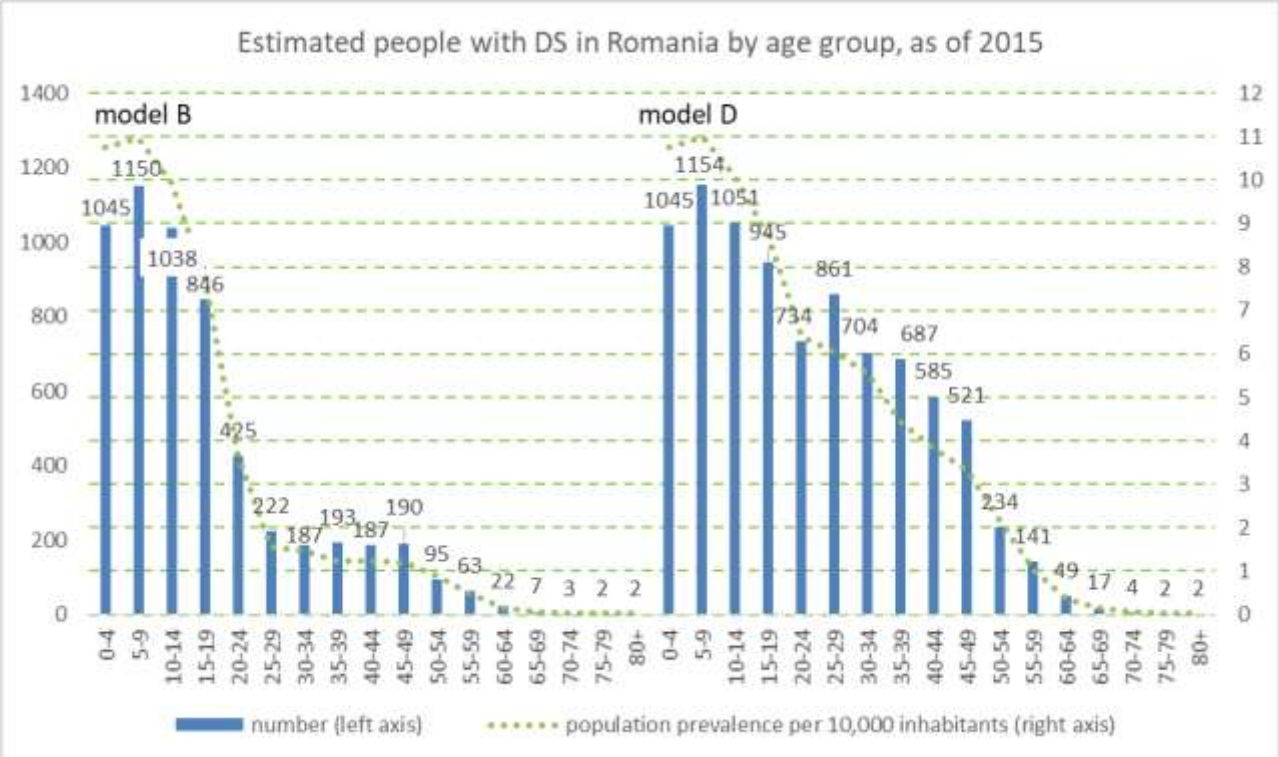

Estimated reduction in LBs with DS as a result of elective terminations in Romania
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

Model A projects 14,233 people with DS alive in 2015, which corresponds to a population prevalence of 7.2 people with DS per 10,000 inhabitants. Model C projects 13,245 (6.7 per 10,000). We consider Model B or D more likely. Model B fits the data on number of people alive, as of 2015, as reported by the General Directorates of Social Assistance and Child Protection (corrected for under-ascertainment) (see S5A). However, under-ascertainment in the older age groups might be larger than in younger people. Model B and D seem to have the best fit as regards age distribution of deaths with DS from national statistics (see S5C) for 2005–2015; Model D seems to have the best fit for 1999–2009.

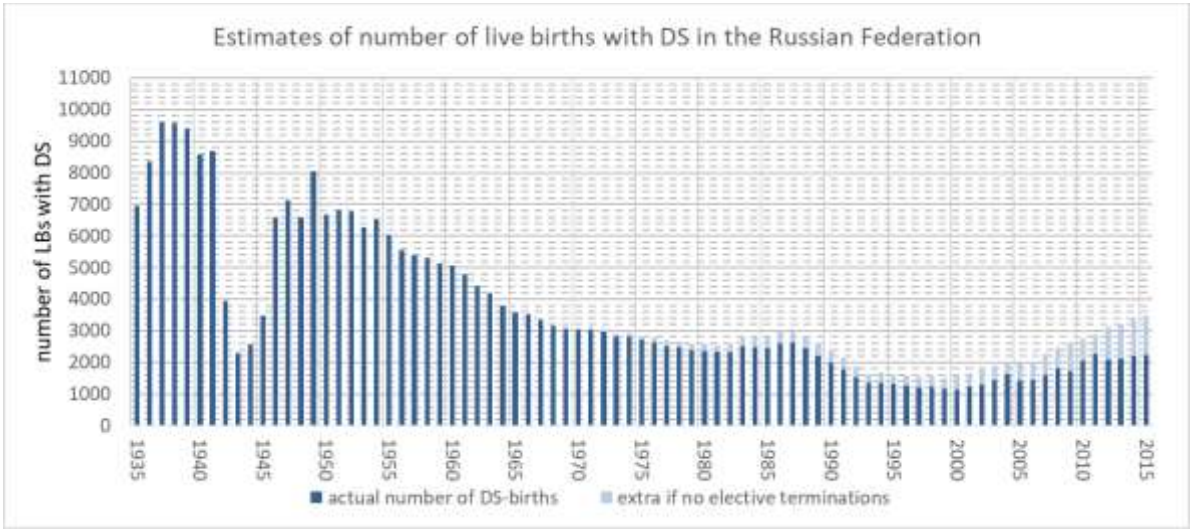


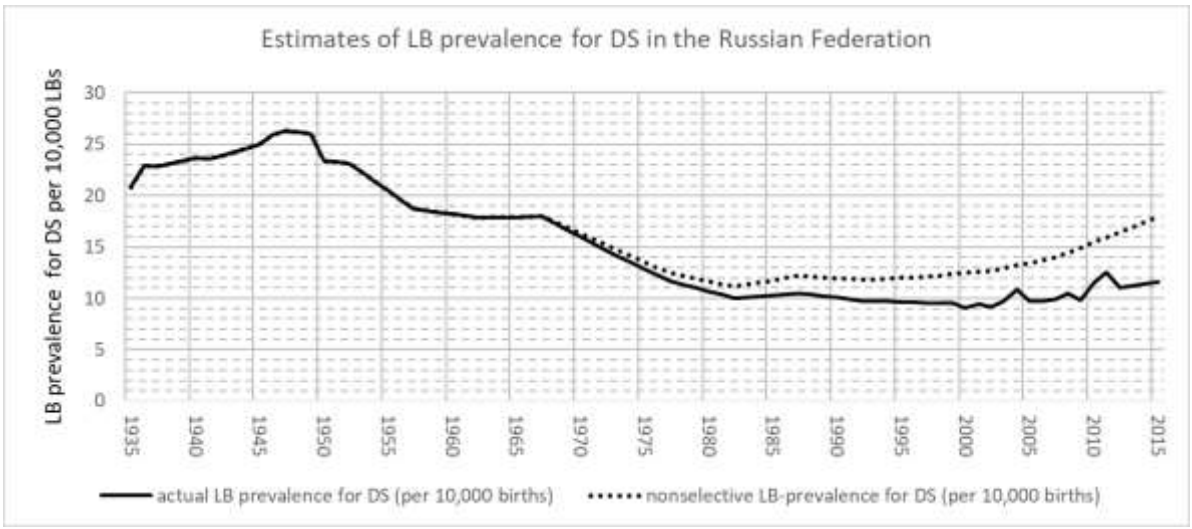


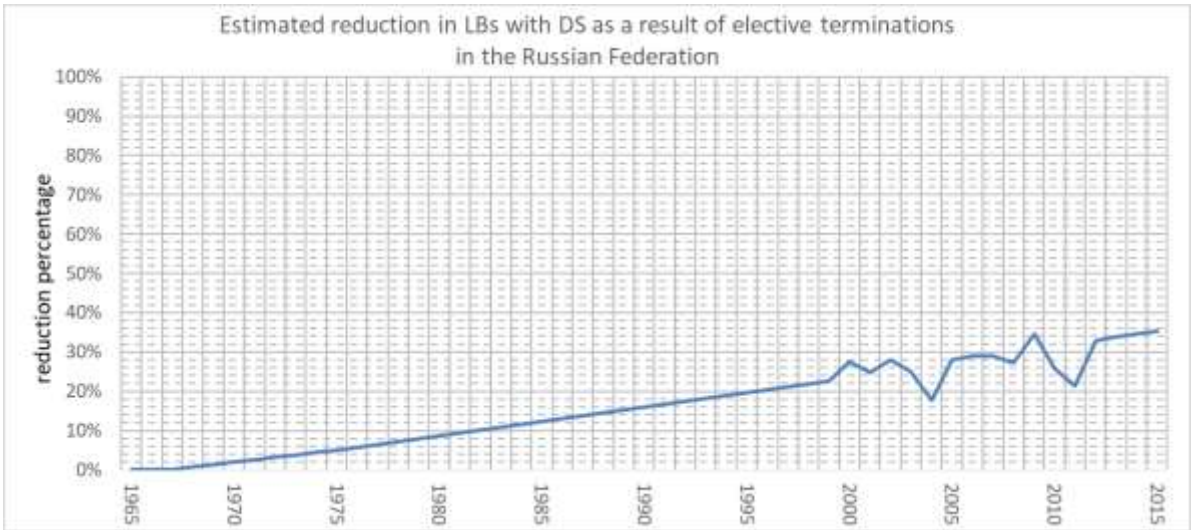

Estimated people with DS in Romania, 1950-2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Romania by age group, as of 2015
model B
model D
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

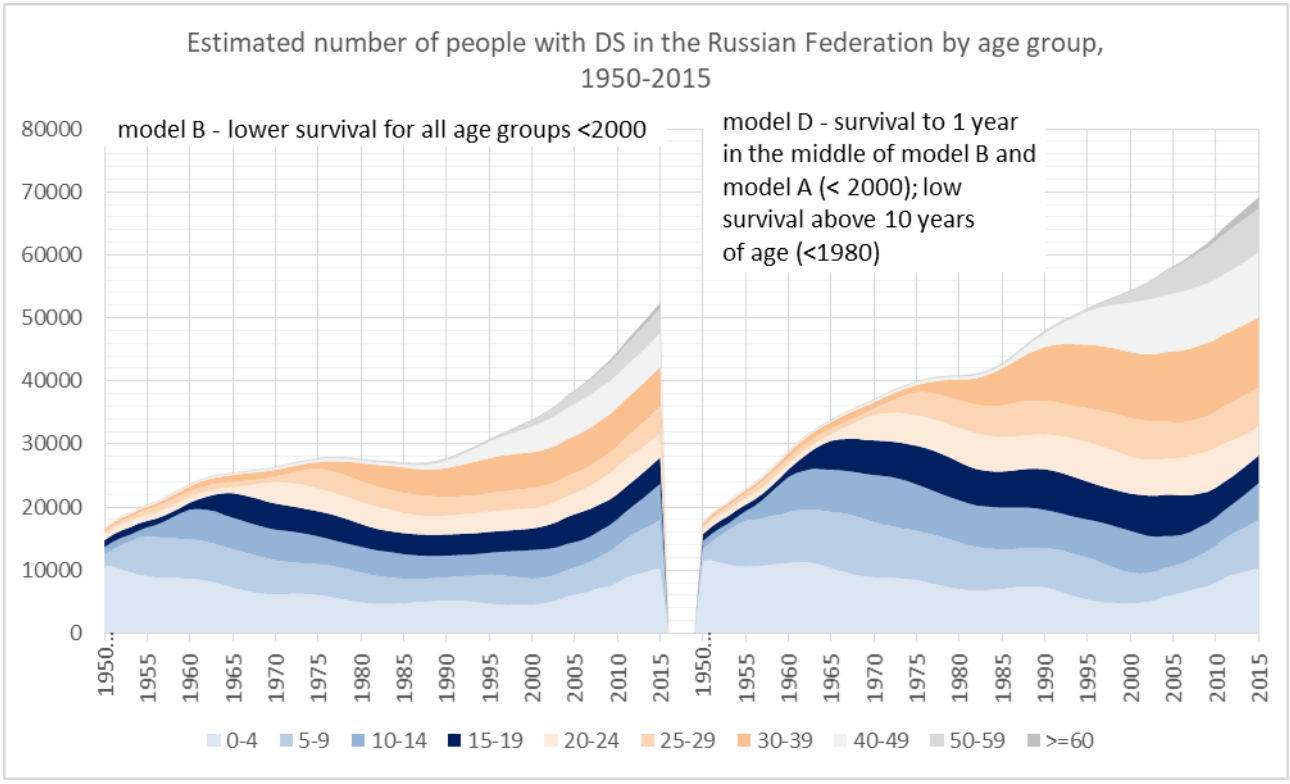
Russian Federation

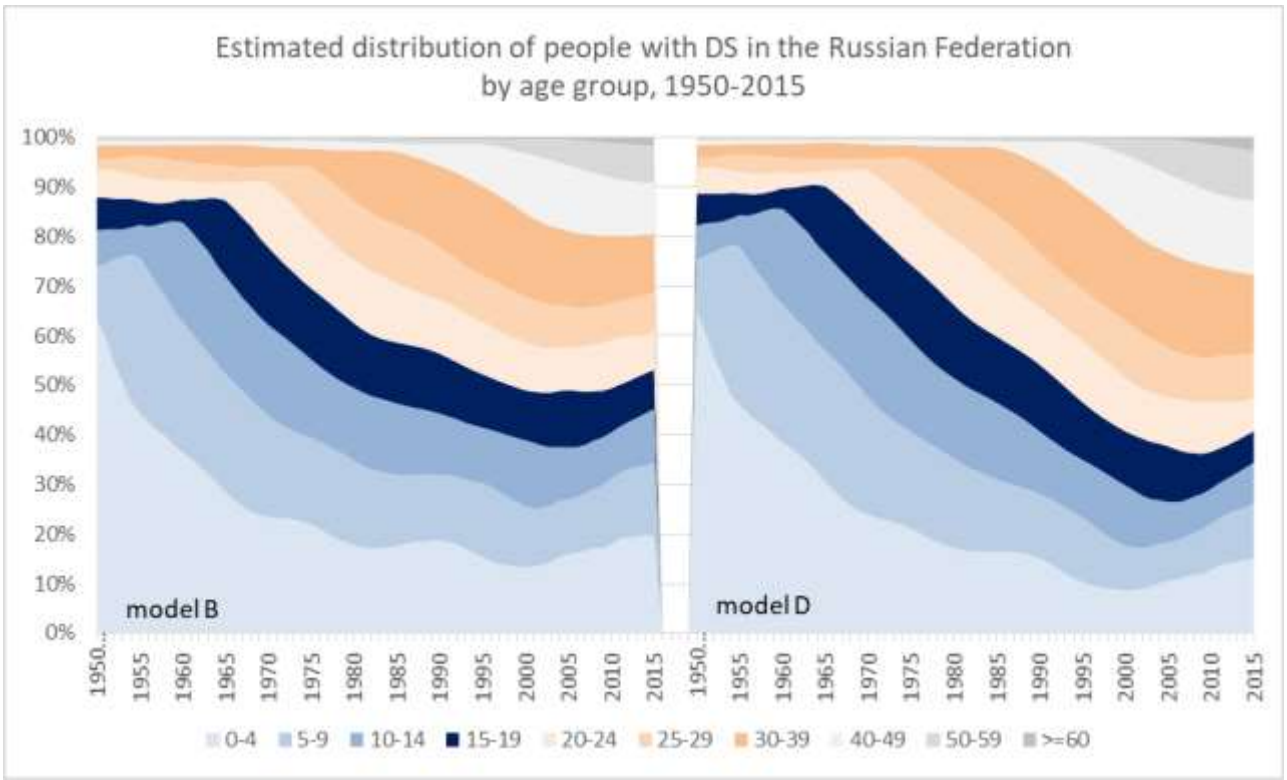


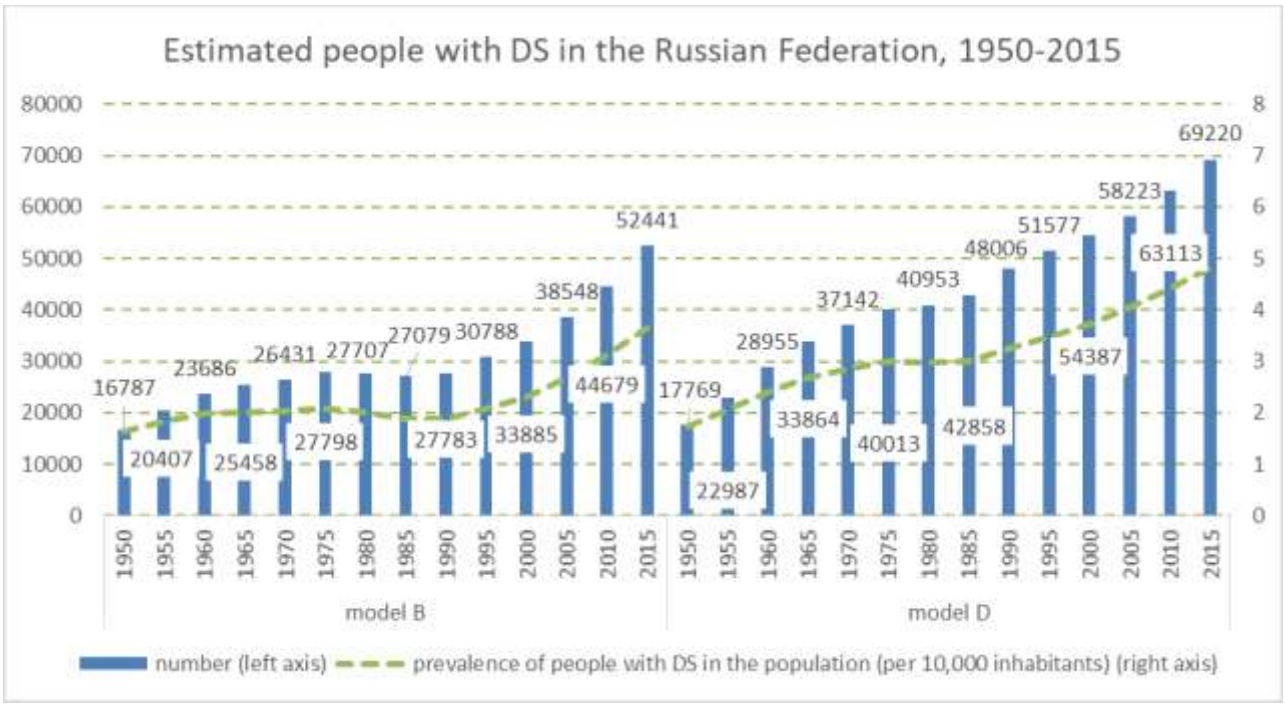


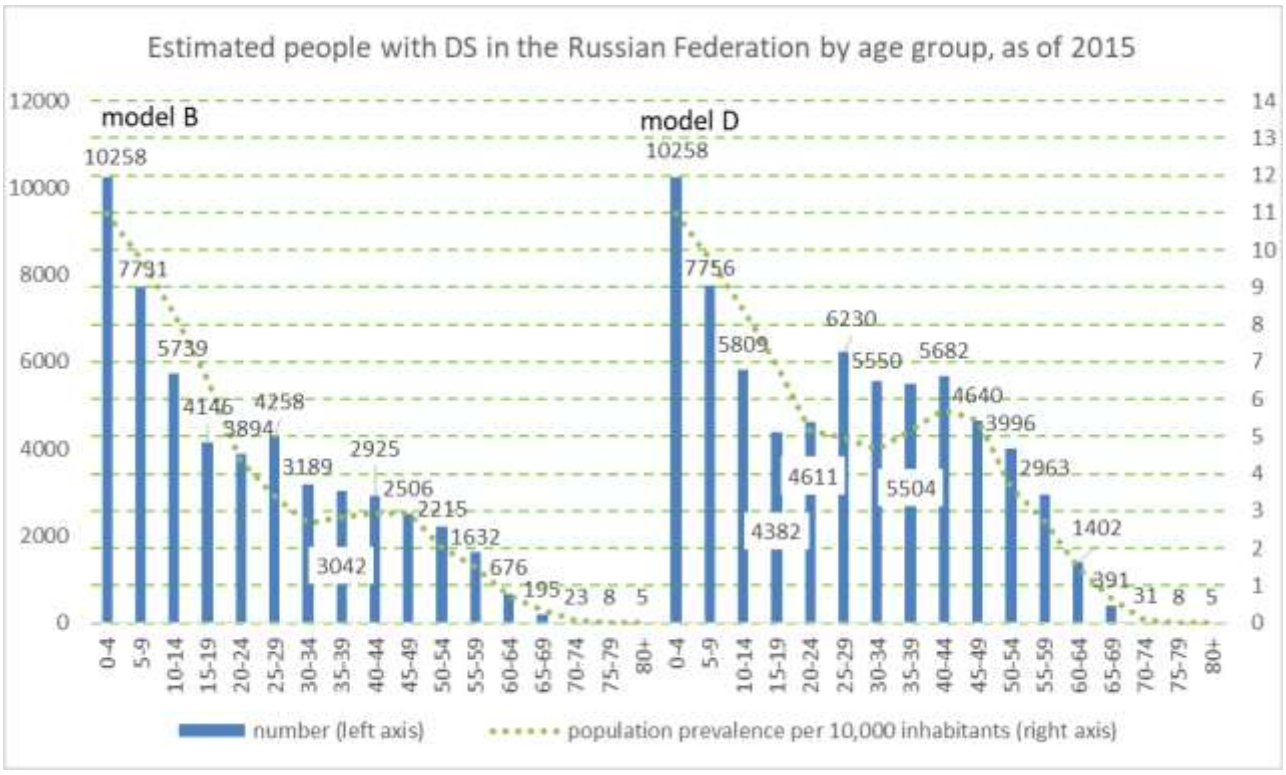


Model A projects 93,828 people with DS alive in 2015, which corresponds to a population prevalence of 6.5 people with DS per 10,000 inhabitants. Model C projects 83,818 (5.8 per 10,000). However, we consider Model B or Model D more likely for former East bloc countries. For the Russian Federation, there is no info on deaths with DS from national statistics.

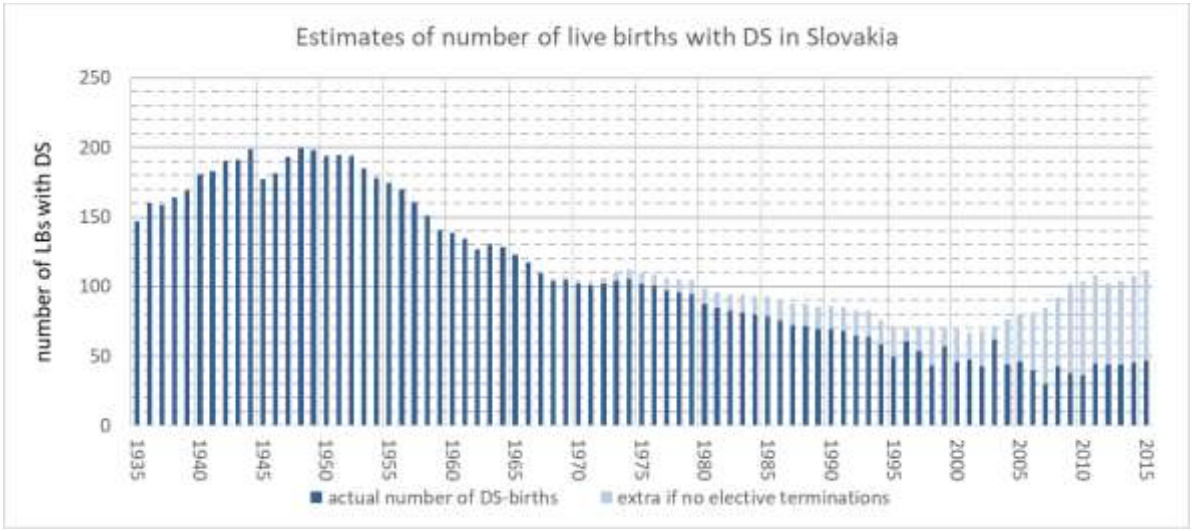


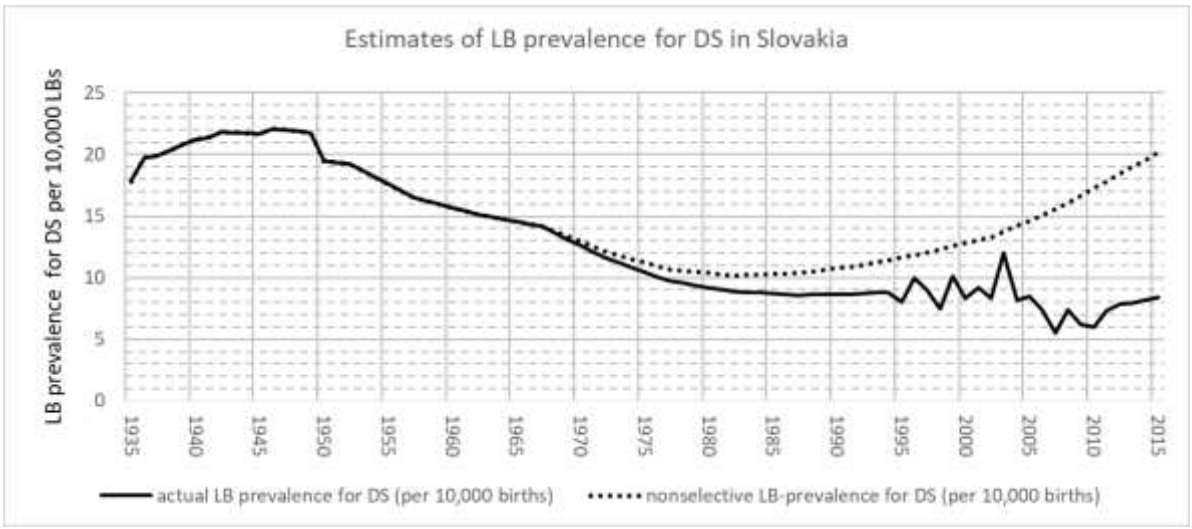


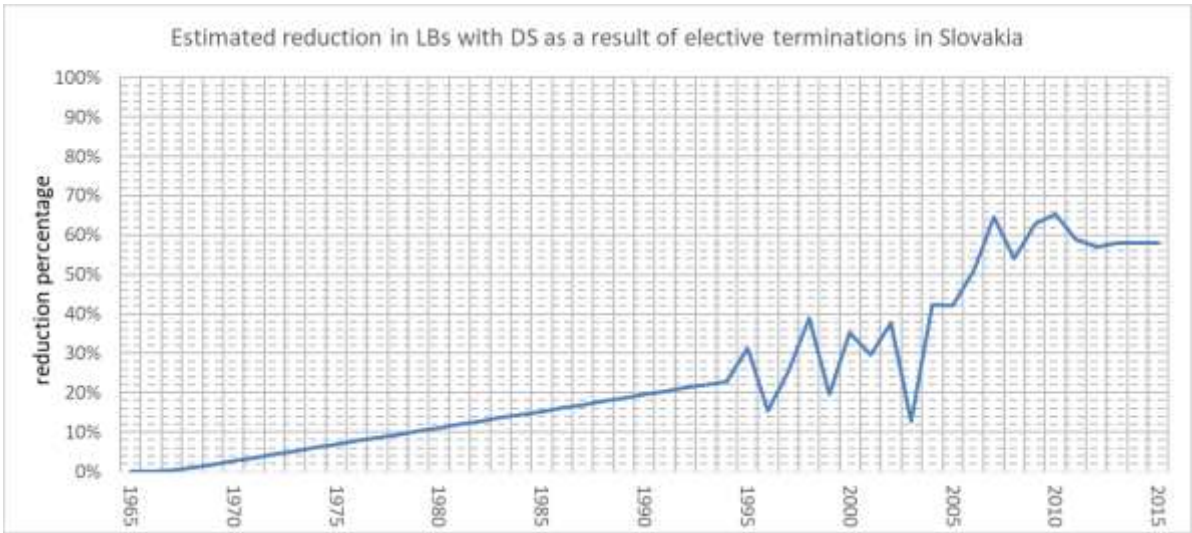

Estimated people with DS in the Russian Federation, 1950-2015
80000
70000
60000
50000
40000
30000
20000
10000
0
8
7
6
5
4
3
2
1
0
16787
20407
23686
25458
26431
27798
27707
27783
27079
33885
30788
38548
44679
52441
17769
22987
28955
33864
37142
40013
40953
42858
48006
54387
51577
58223
63113
69220
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in the Russian Federation by age group, as of 2015
model B
model D
12000
10000
8000
6000
4000
2000
0
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
10258
7791
5739
4146
3894
4258
3189
3042
2925
2506
2215
1632
676
195
23
8
5
10258
7756
5809
4382
4611
6230
5550
5504
5682
4640
3996
2963
1402
391
31
8
5
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

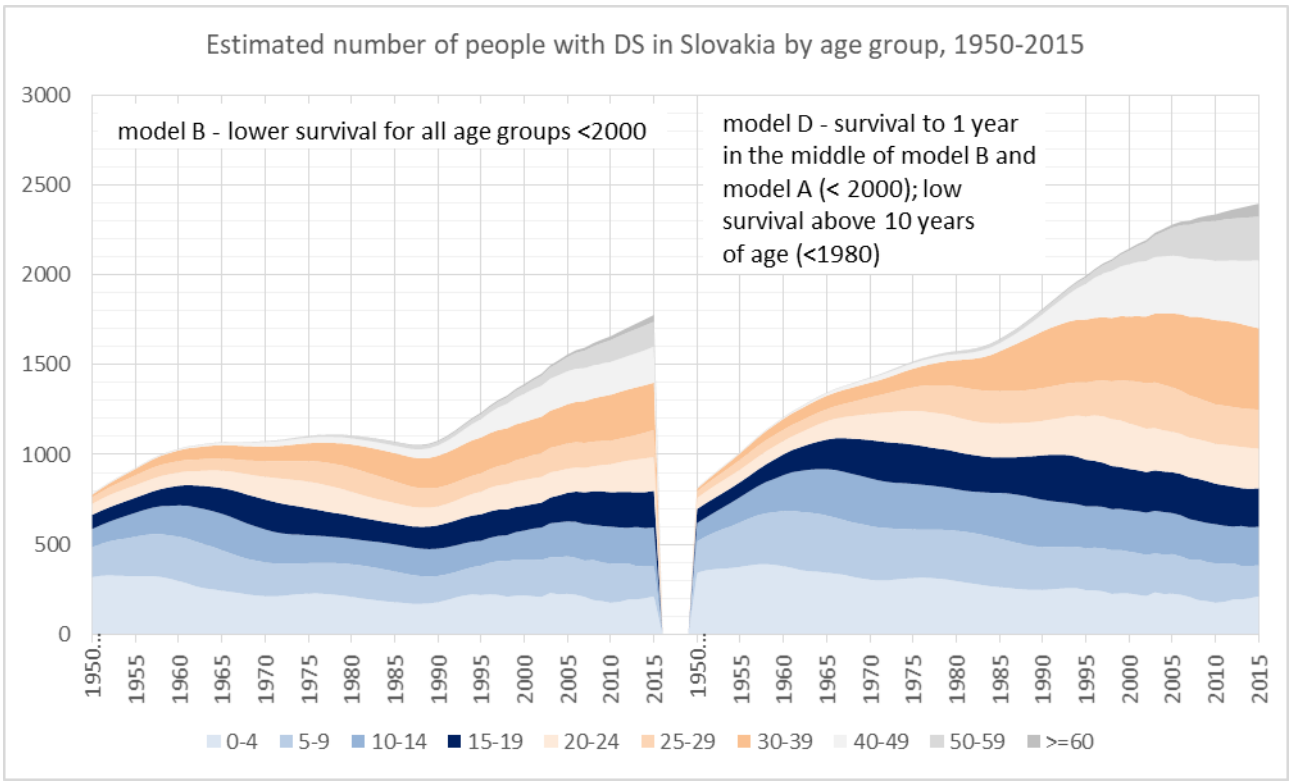
Slovakia

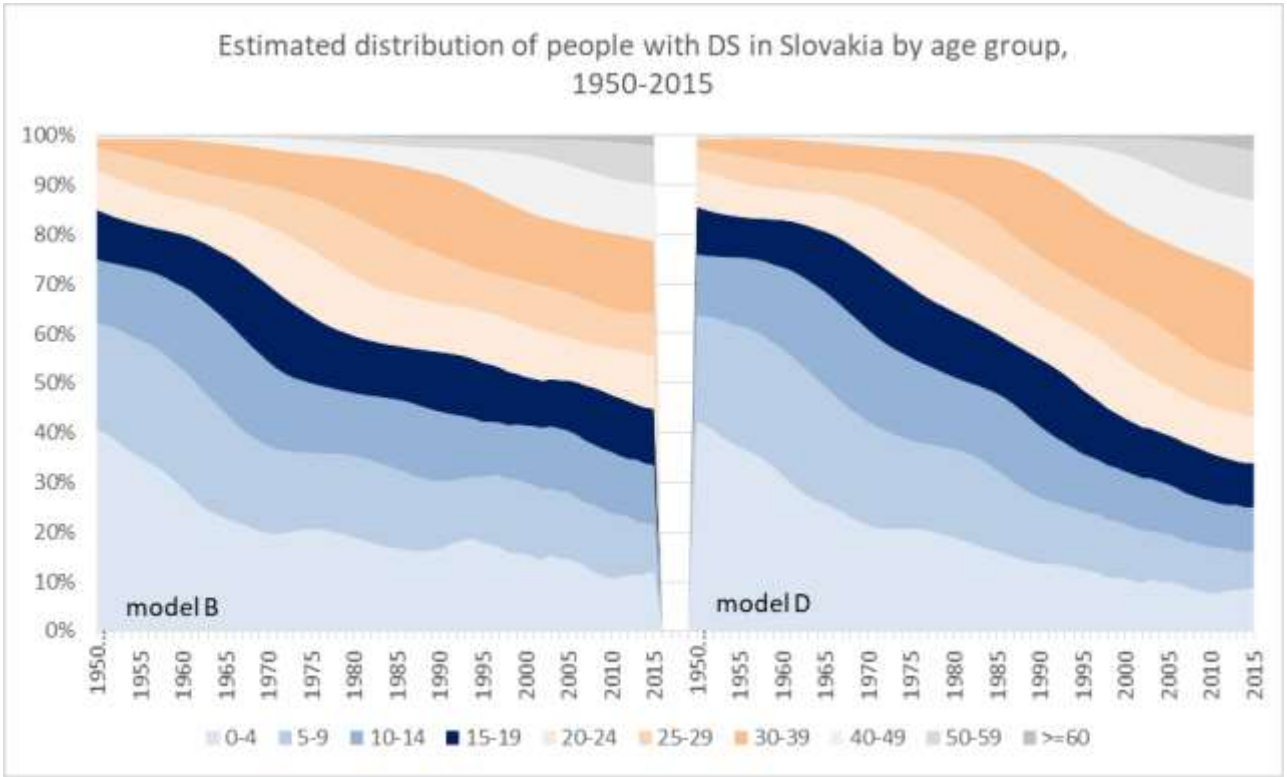

Estimates of number of live births with DS in Slovakia
number of LBs with DS
250
200
150
100
50
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

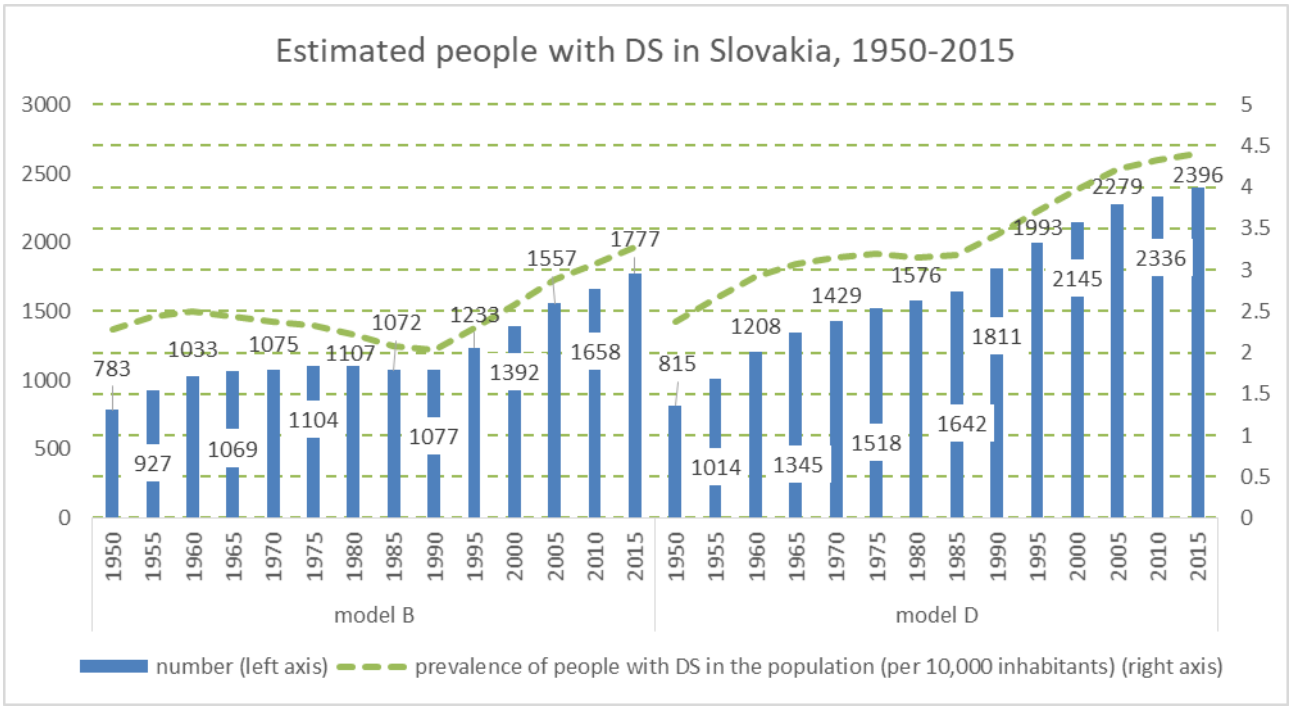

Estimates of LB prevalence for DS in Slovakia
LB prevalence for DS per 10,000 LBs
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)

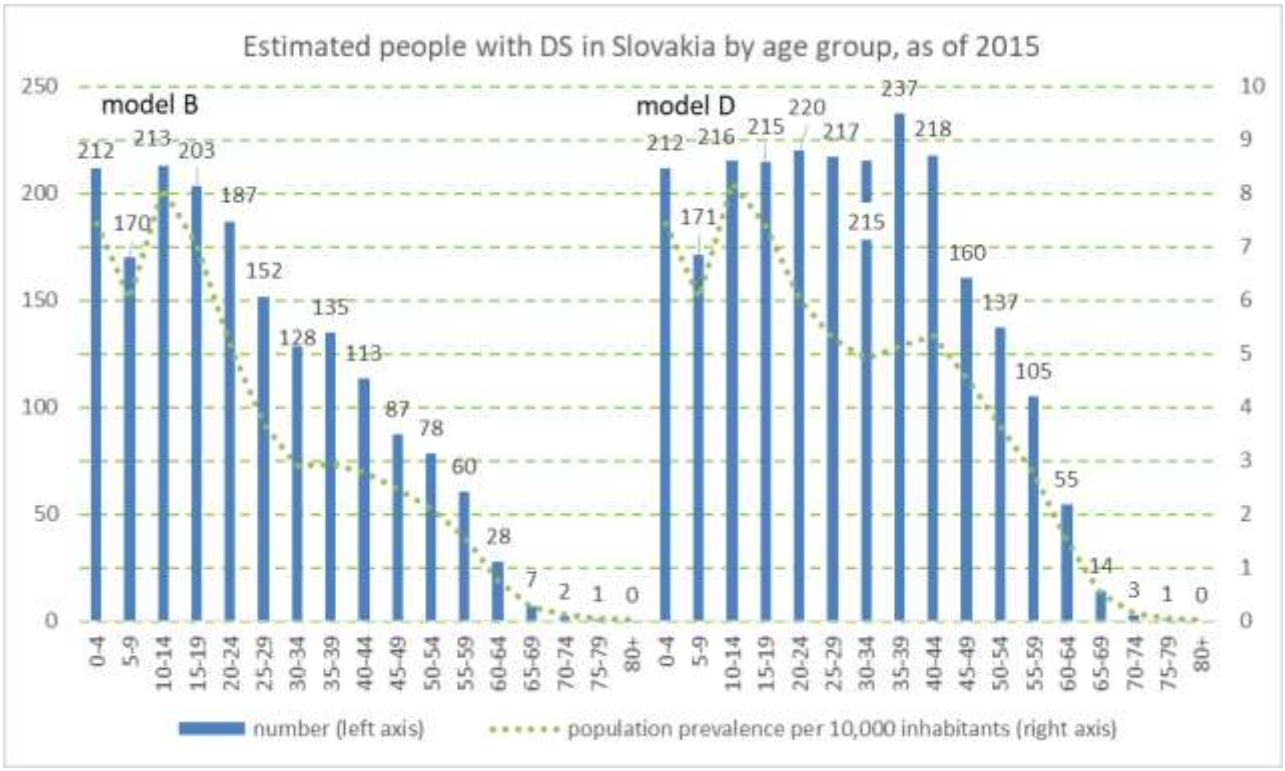

Estimated reduction in LBs with DS as a result of elective terminations in Slovakia
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

Model A projects 3,291 people with DS alive in 2015, which corresponds to a population prevalence of 6.1 people with DS per 10,000 inhabitants. However, model A is unlikely, as it does not fit the data on age distribution of deaths with DS (see S5C). Model C projects 2,929 (5.4 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. For Slovakia, Model B seems to have a better fit with the age distribution of deaths with DS as reported in the national statistics (see S5C).

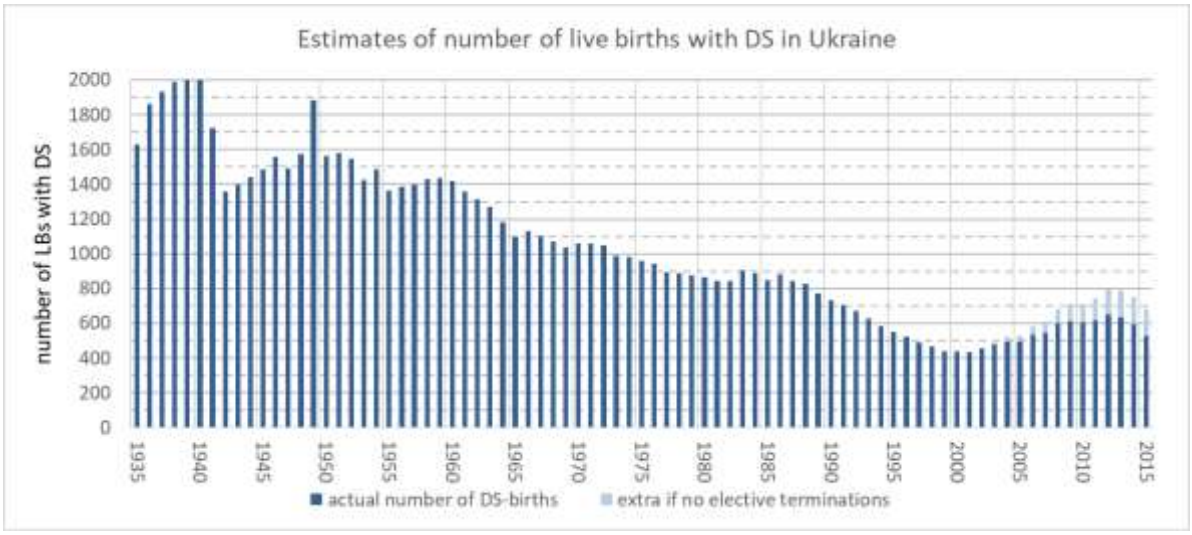


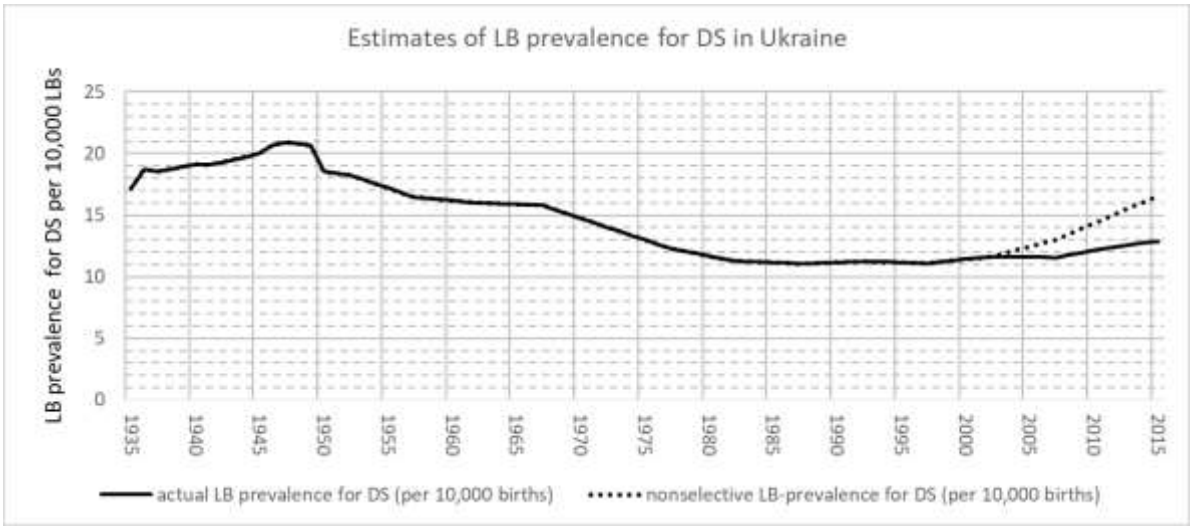


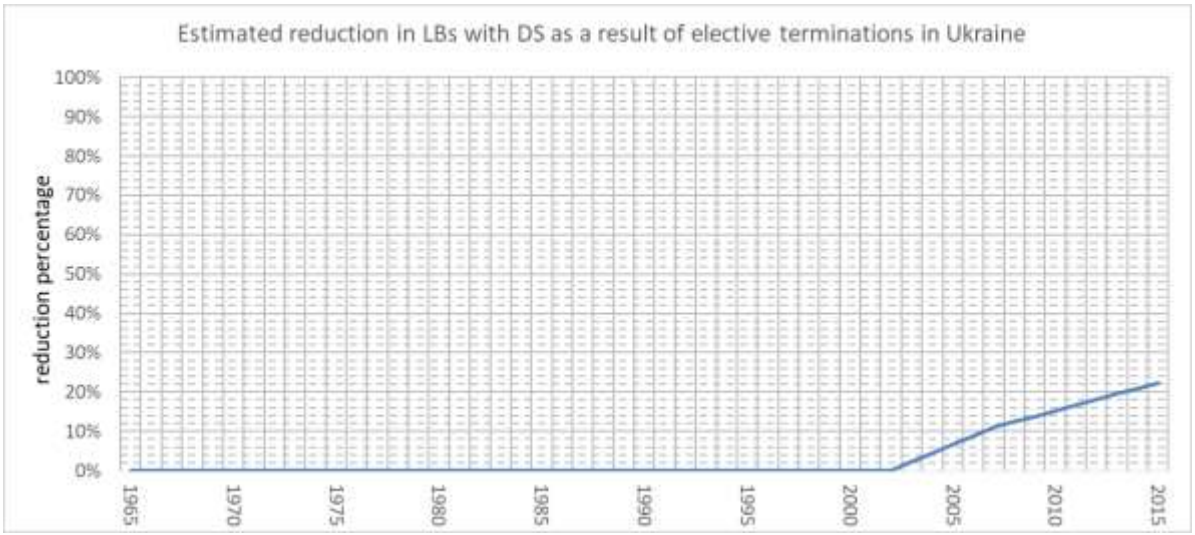

Estimated people with DS in Slovakia, 1950-2015
3000
2500
2000
1500
1000
500
0
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
783
927
1033
1069
1075
1104
1107
1072
1077
1233
1392
1557
1658
1777
815
1014
1208
1345
1429
1518
1576
1642
1811
1993
2145
2279
2336
2396
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Slovakia by age group, as of 2015
250
200
150
100
50
0
10
9
8
7
6
5
4
3
2
1
0
model B
212 213 203 187 152 135 113 87 78 60 28 7 2 1 0
model D
212 216 215 220 217 215 237 218 160 137 105 55 14 3 1 0
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

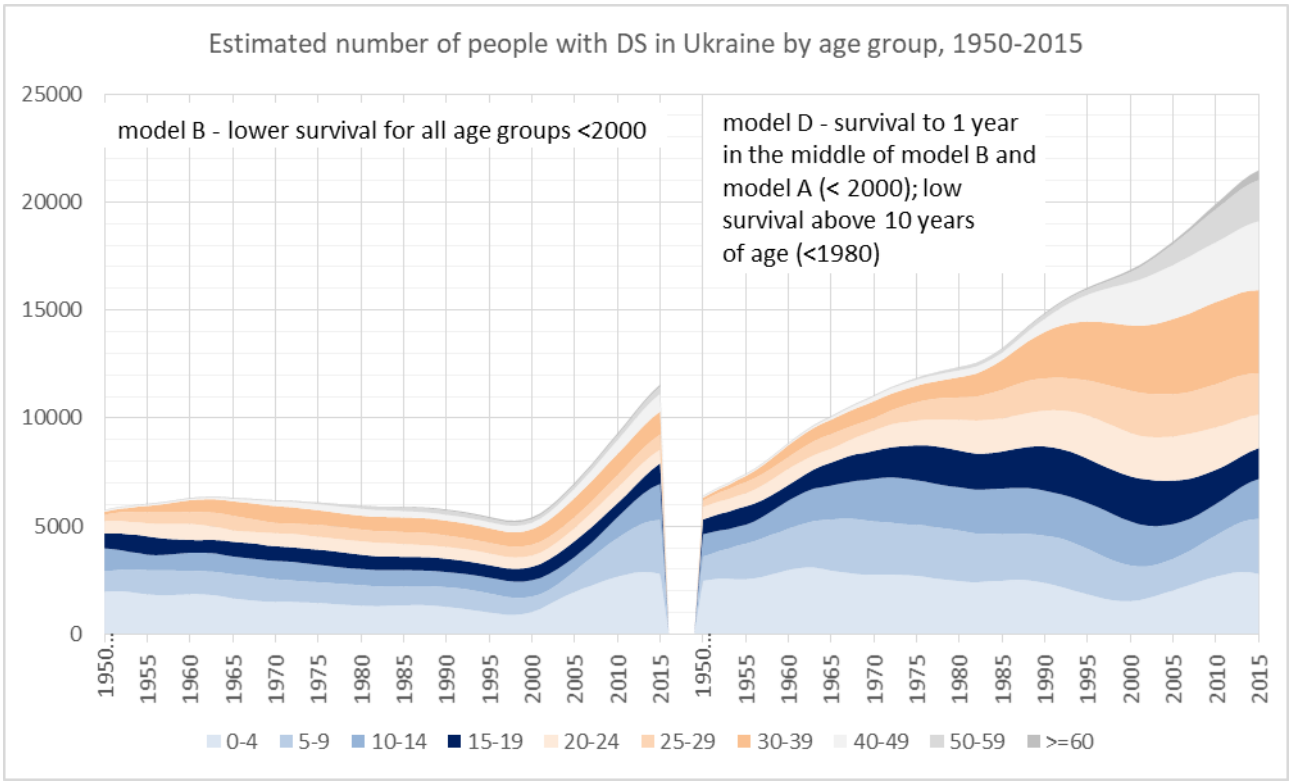
Ukraine

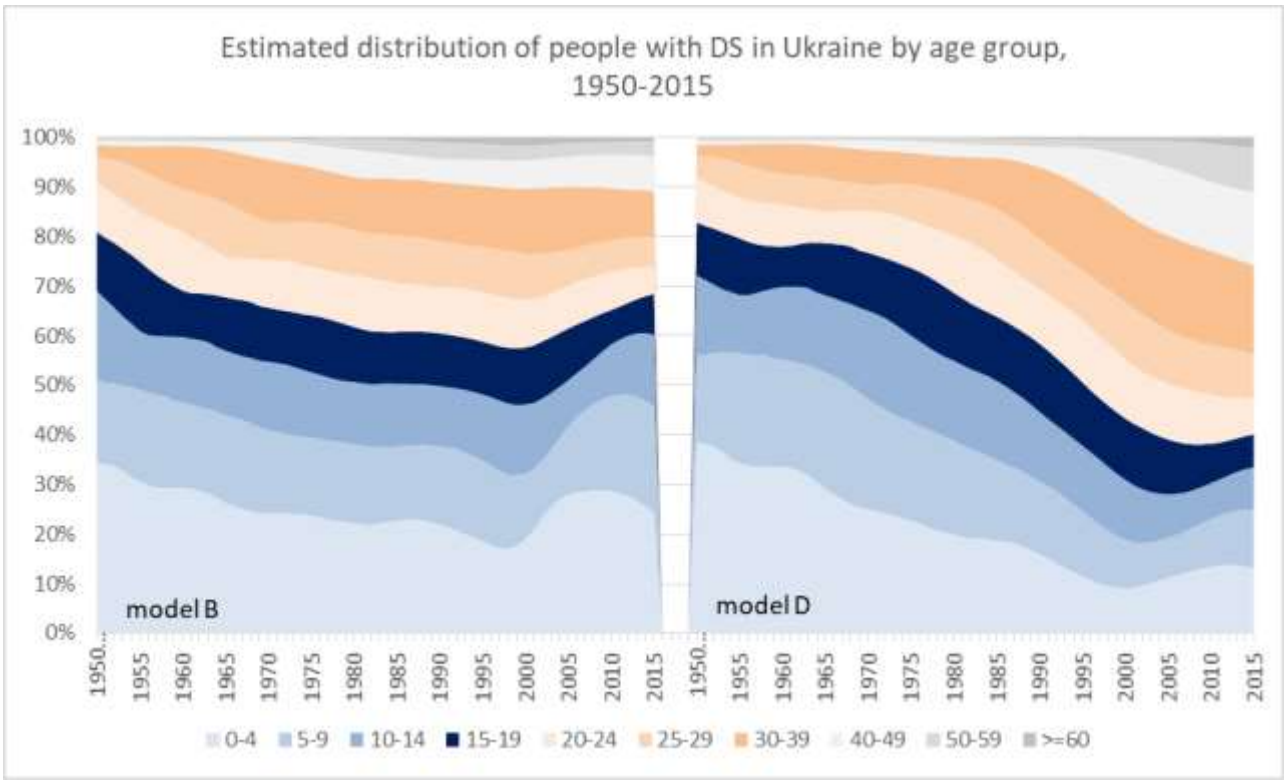

Estimates of number of live births with DS in Ukraine
number of LBs with DS
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual number of DS-births
extra if no elective terminations

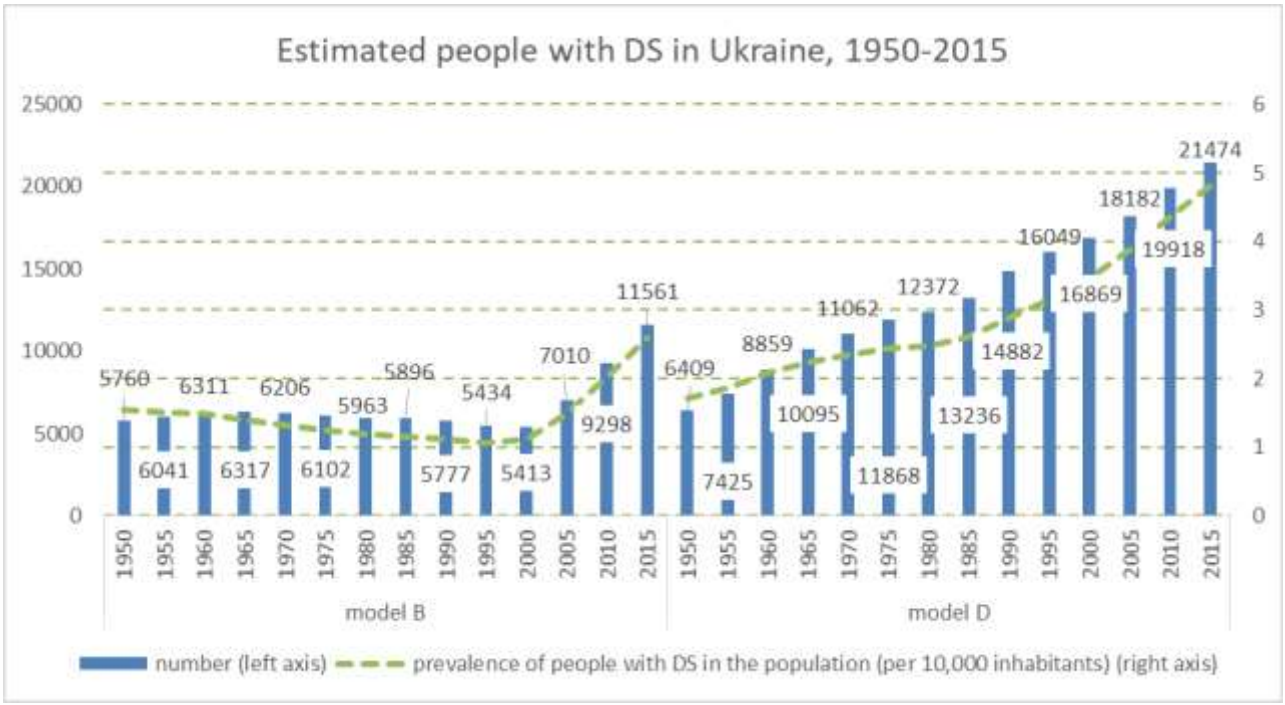

Estimates of LB prevalence for DS in Ukraine
LB prevalence for DS per 10,000 LBs
25
20
15
10
5
0
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
actual LB prevalence for DS (per 10,000 births)
nonselective LB-prevalence for DS (per 10,000 births)

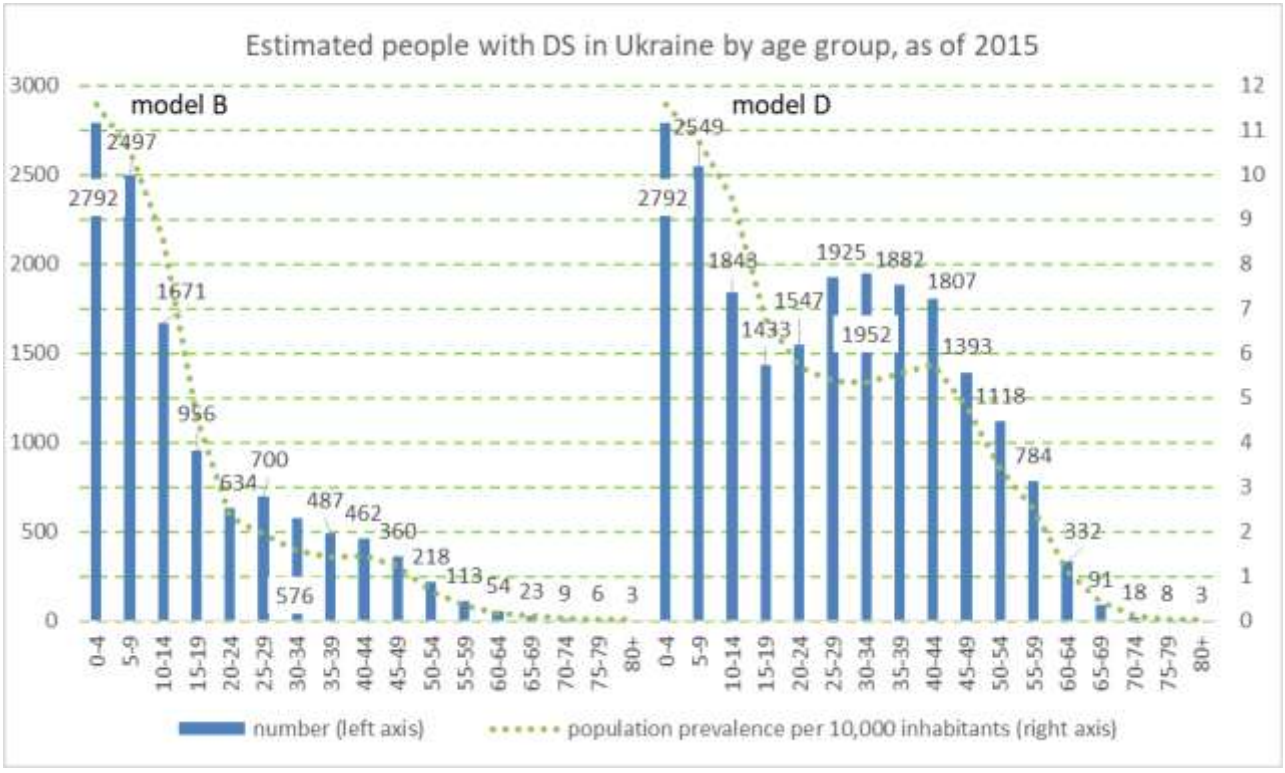

Estimated reduction in LBs with DS as a result of elective terminations in Ukraine
reduction percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015

Model A projects 33,190 people with DS alive in 2015, which corresponds to a population prevalence of 7.4 people with DS per 10,000 inhabitants. Model C predicts 29,930 (6.7 per 10,000). However, we consider Models B or D more likely. Model B fits the data on number of people alive in Ukraine (0–17 years), as of 2015, as reported by the Ministry of Health protection (corrected for under-ascertainment) (see S5A). However, it is possible that under-ascertainment in the older age groups is larger than in younger people with DS, which would be the case if Model D is correct. For Ukraine, there is no info on deaths with DS from national statistics.






Estimated people with DS in Ukraine, 1950-2015
25000
20000
15000
10000
5000
0
6
5
4
3
2
1
0
5760
6041
6311
6317
6206
6102
5963
5896
5777
5434
5413
7010
9298
11561
6409
7425
8859
10095
11062
11868
12372
13236
14882
16049
16869
18182
19918
21474
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Ukraine by age group, as of 2015
3000
2500
2000
1500
1000
500
0
12
11
10
9
8
7
6
5
4
3
2
1
0
model B
model D
2792
2497
1671
956
634
700
576
487
462
360
218
113
54
23
9
6
3
2792
2549
1843
1547
1433
1925
1952
1882
1807
1393
1118
784
332
91
18
8
3
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Changes in LB prevalence of DS between 1981–1985 and 2011–2015

In the Table below, nonselective and actual LB prevalence for DS are presented for 1981–1985 and 2011–2015. We also have estimated the magnitude of change in this period. With the exception of Albania, nonselective prevalence has increased in all countries under observation. In Ireland and Malta, abortions are highly restricted by legal regulations. Out of 37 European countries permitting abortions, in 11 European countries (and in the U.S.), actual LB prevalence increased, but to a much smaller extent than nonselective LB prevalence; in the other 26 European countries actual LB prevalence decreased. For Europe as a whole, nonselective LB prevalence rose with 73.5%, whereas actual LB prevalence fell with 11.7%.

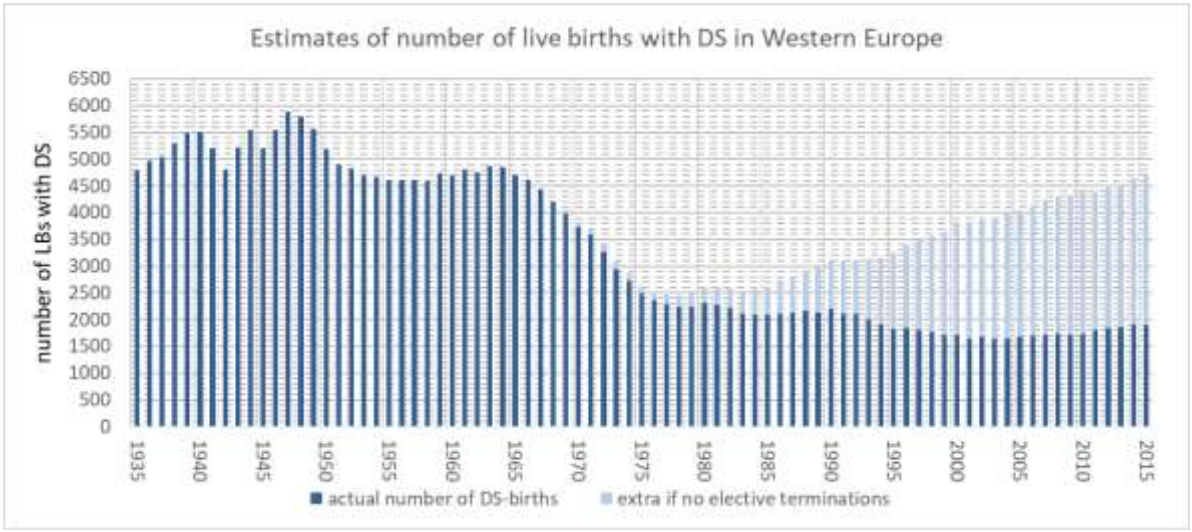
Country	Nonselective live birth prevalence 1981-1985	Nonselective live birth prevalence 2011-2015	Actual live birth prevalence 1981-1985	Actual live birth prevalence 2011-2015	Change in nonselective live birth prevalence (%)	Change in actual live birth prevalence (%)
Ireland *	19.46	30.07	19.46	27.80	54.5%	42.8%
Malta *	17.40	20.12	17.40	20.12	15.6%	15.6%
Hungary	10.75	23.14	7.80	8.97	115.2%	15.1%
Germany	12.07	24.42	10.69	12.21	102.3%	14.2%
Russian Federation	11.44	16.94	10.20	11.54	48.2%	13.0%
Ukraine	11.27	15.62	11.27	12.59	38.7%	11.7%
Croatia	11.30	20.24	11.30	12.29	79.0%	8.8%
Sweden	15.05	23.95	13.19	14.29	59.1%	8.4%
United Kingdom	12.95	22.55	9.56	10.32	74.1%	8.0%
Norway	13.23	22.48	11.37	12.13	70.0%	6.7%
Serbia	13.22	18.12	13.22	13.89	37.1%	5.1%
Netherlands	12.79	22.51	11.47	12.02	76.0%	4.7%
Republic of Moldova	12.24	13.42	12.24	12.29	9.6%	0.3%
Romania	11.68	17.02	11.68	11.40	45.8%	-2.4%
Luxembourg	12.74	27.03	10.38	9.68	112.2%	-6.8%
North Macedonia	11.42	16.01	10.46	9.64	40.2%	-7.8%
Switzerland	13.61	26.56	10.36	9.44	95.1%	-8.9%
Austria	12.67	23.01	9.88	8.89	81.6%	-10.0%
Slovakia	10.24	18.95	8.85	7.95	85.0%	-10.1%
Belgium	11.74	23.27	7.97	7.08	98.2%	-11.2%
Finland	15.32	22.43	12.39	10.30	46.3%	-16.9%
Greece	12.65	27.66	12.16	9.44	118.7%	-22.4%
Belarus	11.25	15.31	11.25	8.23	36.0%	-26.8%
Bosnia and Herzegovina	12.11	16.89	12.11	8.64	39.6%	-28.6%
Montenegro	13.25	18.89	13.25	9.44	42.5%	-28.8%
Italy	14.77	32.99	13.56	9.62	123.4%	-29.0%
France	12.66	22.21	10.34	7.19	75.4%	-30.5%
Latvia	12.56	21.84	12.56	8.25	73.8%	-34.3%
Lithuania	13.83	17.97	13.83	8.92	29.9%	-35.5%
Poland	12.56	18.35	12.56	7.86	46.1%	-37.4%
Czech Republic	9.99	21.15	7.97	4.83	111.7%	-39.4%
Iceland	13.32	21.96	11.42	6.86	64.9%	-39.9%
Albania	15.93	13.56	15.93	9.02	-14.8%	-43.3%
Denmark	12.57	23.31	8.96	4.88	85.4%	-45.5%
Bulgaria	9.53	17.30	9.29	4.54	81.5%	-51.1%
Slovenia	11.34	20.60	11.20	4.87	81.6%	-56.5%
Estonia	12.19	21.37	12.19	5.16	75.2%	-57.7%
Spain	16.35	33.04	16.14	5.49	102.1%	-66.0%
Portugal	15.36	25.80	14.87	5.05	67.9%	-66.1%
Europe	**12.50**	**21.69**	**11.30**	**10.05**	**73.5%**	**-11.0%**
United States	11.58	19.22	9.94	12.88	66.0%	29.6%

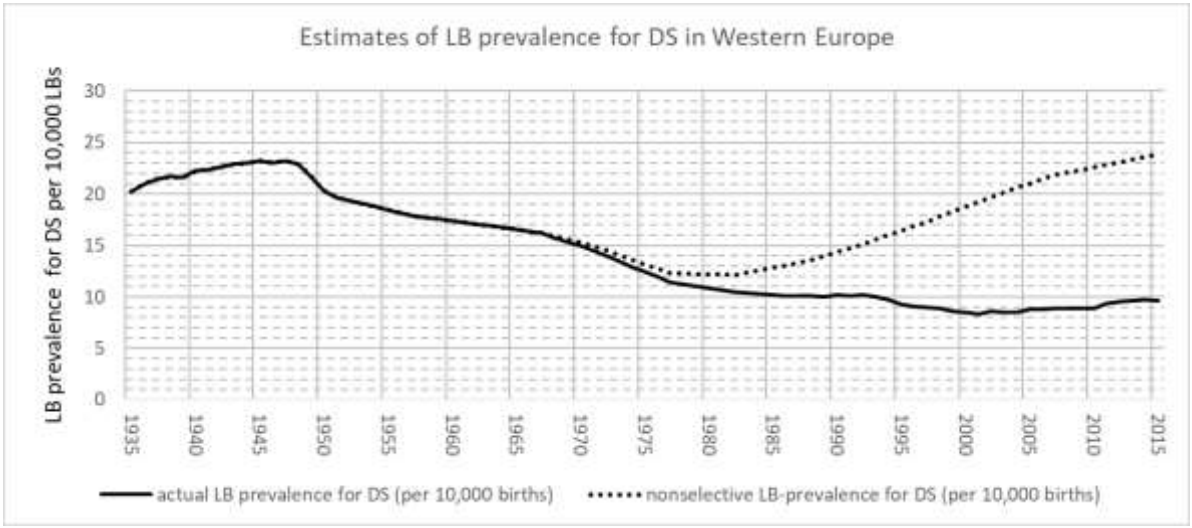
** In Ireland and Malta abortions are highly restricted by legal regulations.*

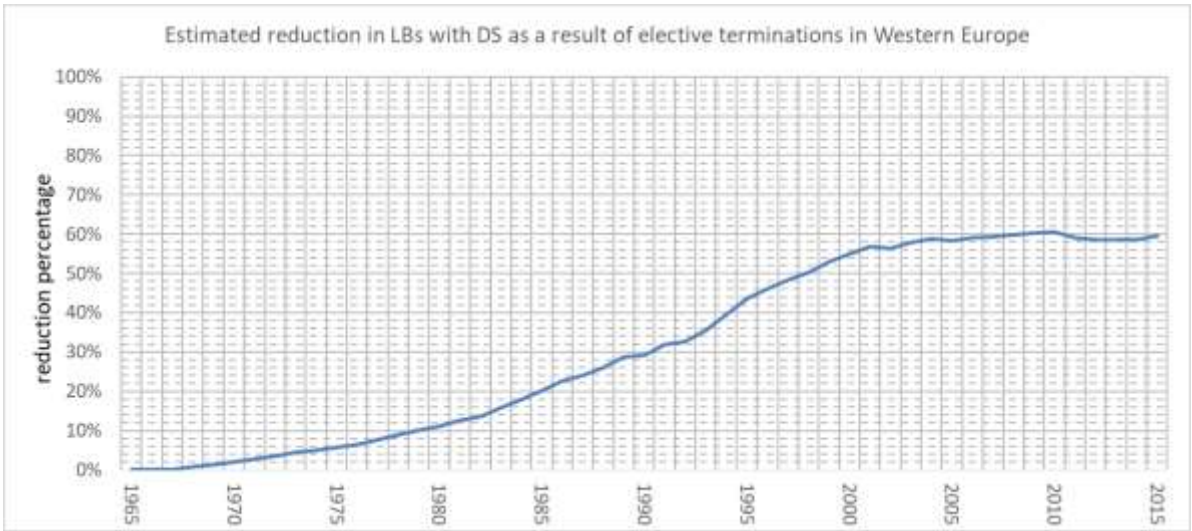
S7. Results by region

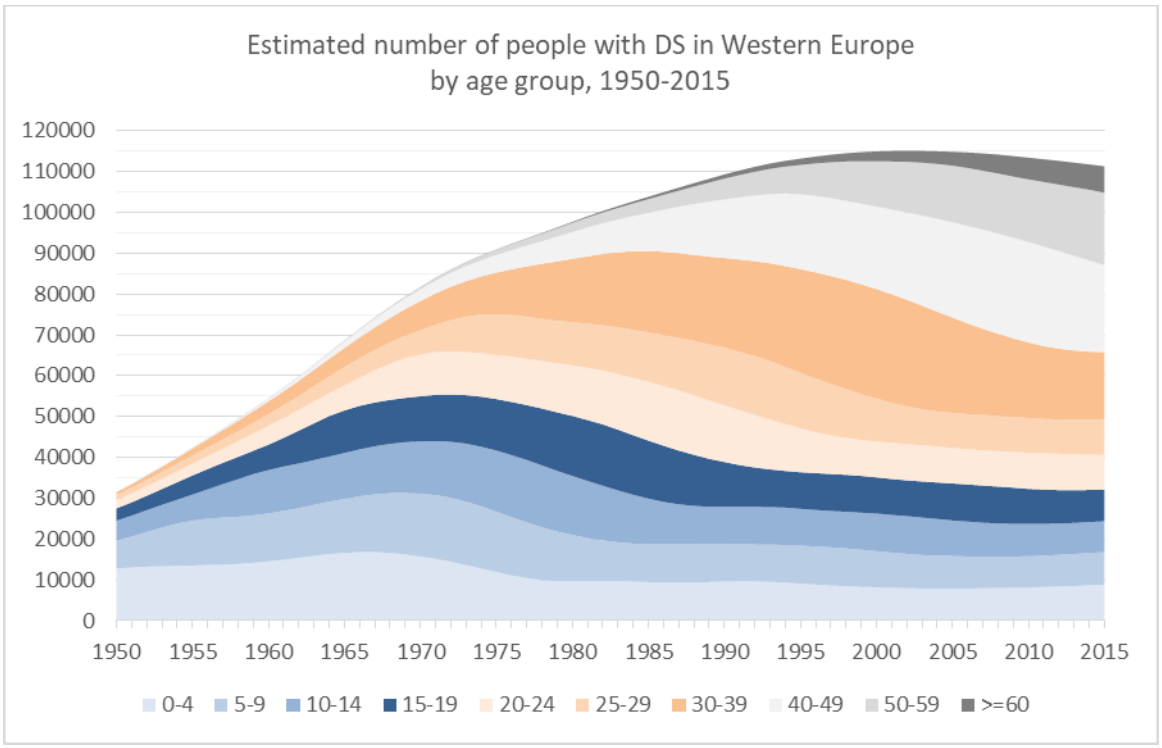
In this section, we present the results pooled by region (Western, Northern, Southern, and Northern Europe; former West bloc; former East bloc; Europe total; Europe some extra graphs)

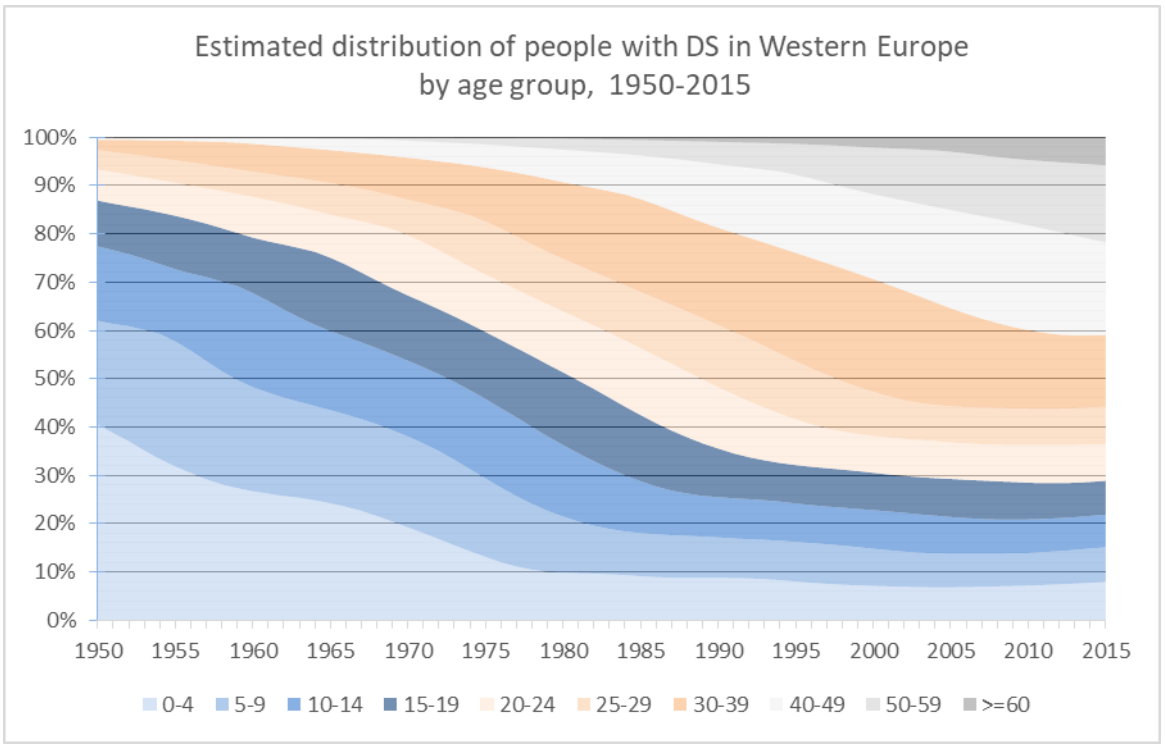
Western Europe

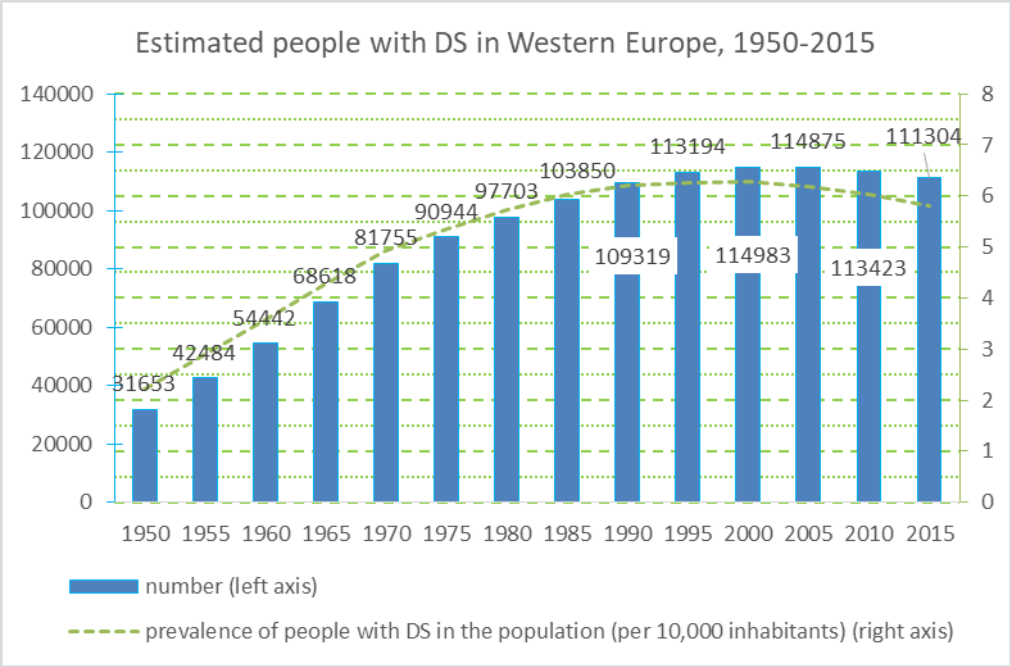


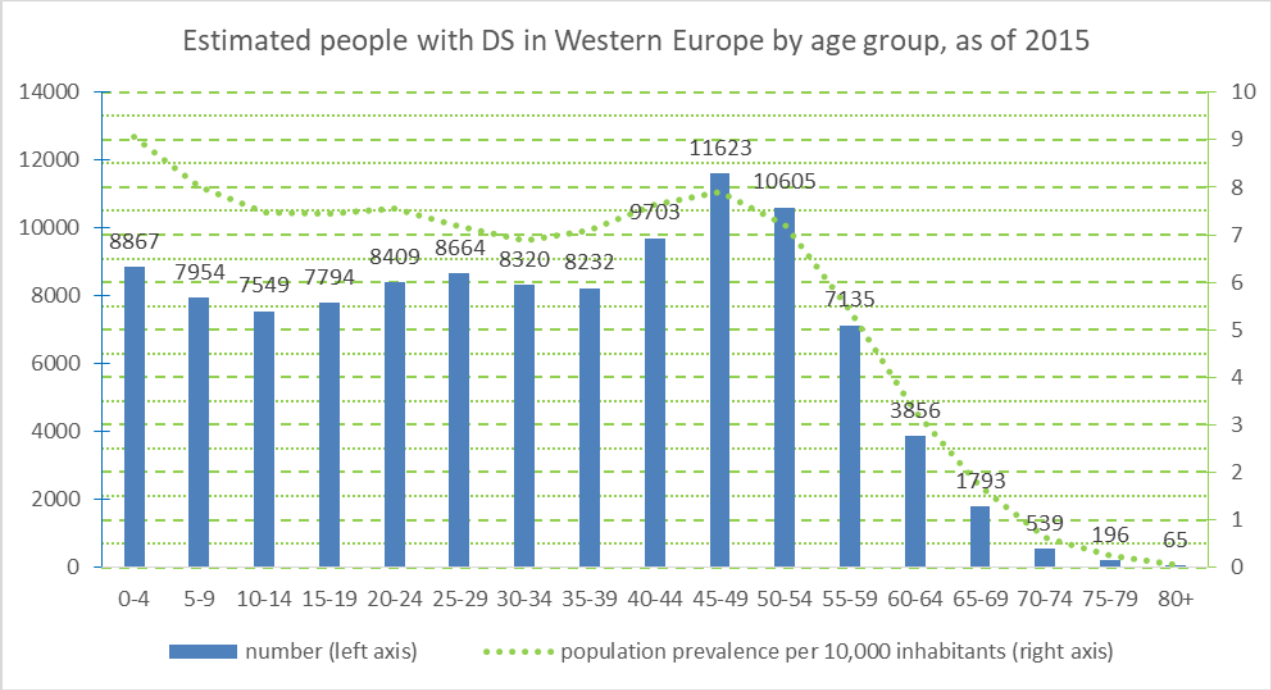




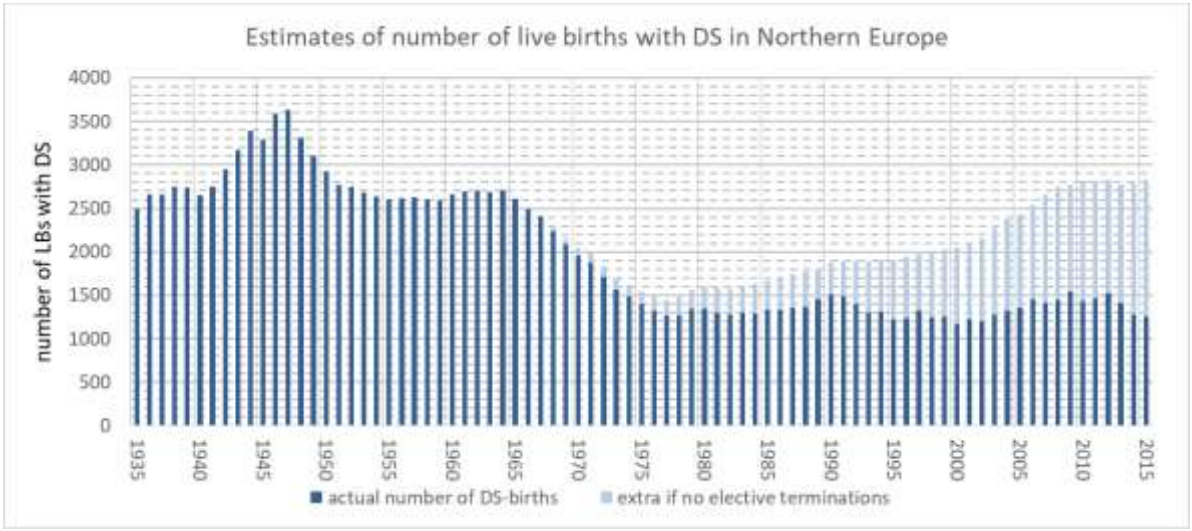

Estimated number of people with DS in Western Europe
by age group, 1950-2015
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

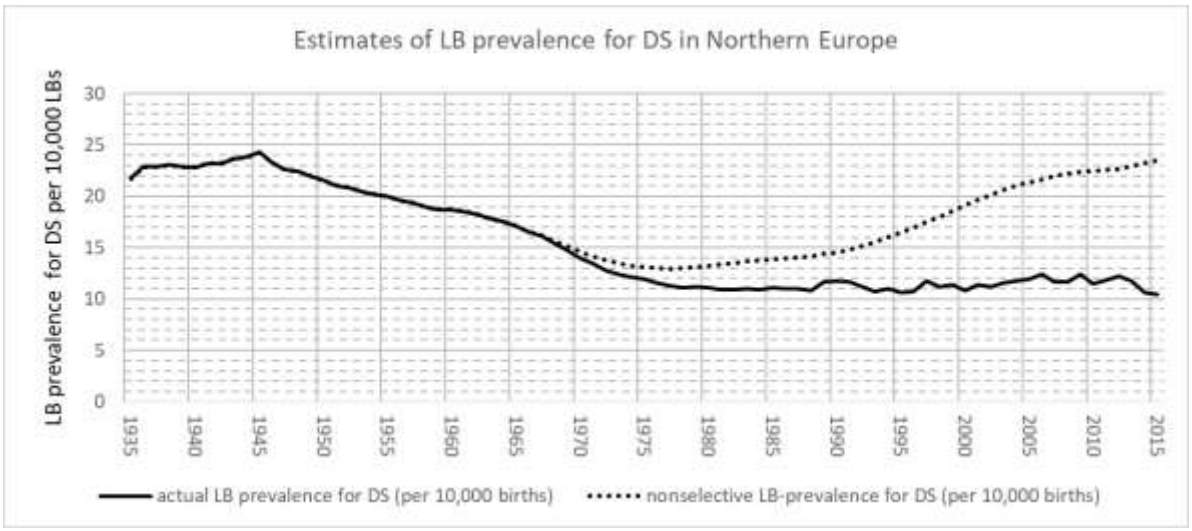

Estimated distribution of people with DS in Western Europe
by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

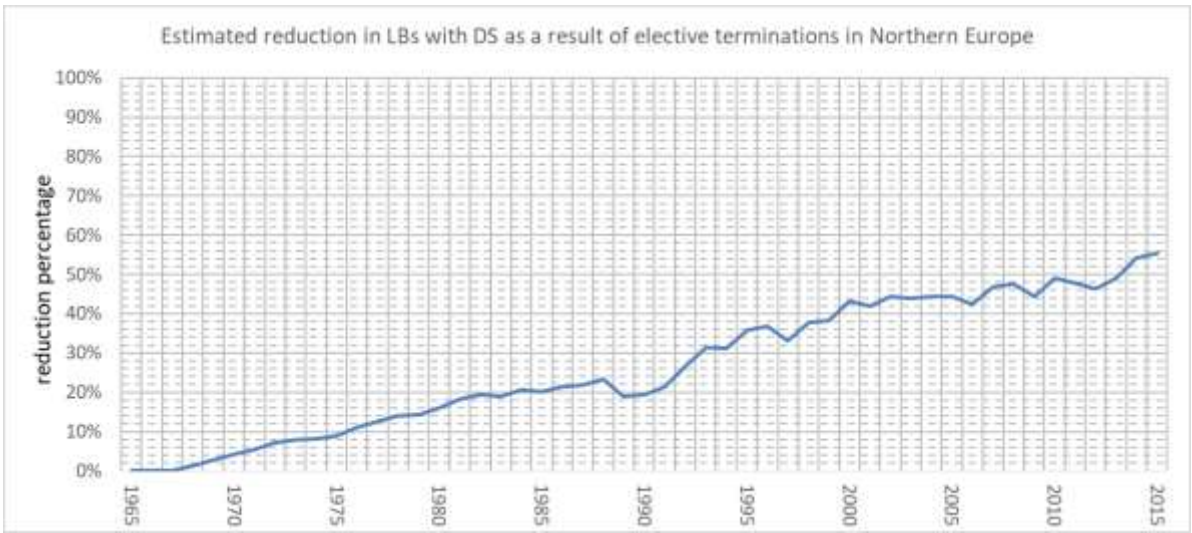

Estimated people with DS in Western Europe, 1950-2015
140000
120000
100000
80000
60000
40000
20000
0
8
7
6
5
4
3
2
1
0
31653
42484
54442
68618
81755
90944
97703
103850
109319
113194
114983
114875
113423
111304
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Western Europe by age group, as of 2015
14000
12000
10000
8000
6000
4000
2000
0
10
9
8
7
6
5
4
3
2
1
0
8867
7954
7549
7794
8409
8664
8320
8232
9703
11623
10605
7135
3856
1793
539
196
65
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

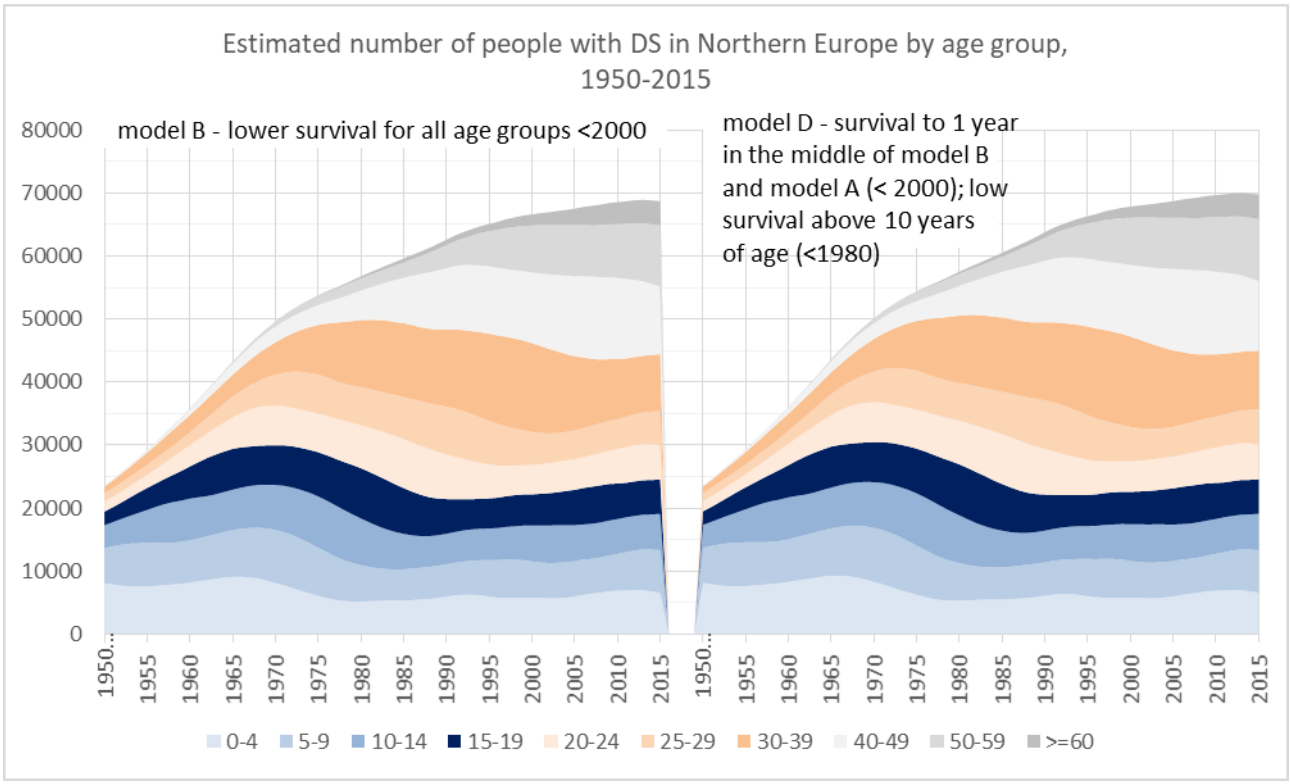
Northern Europe

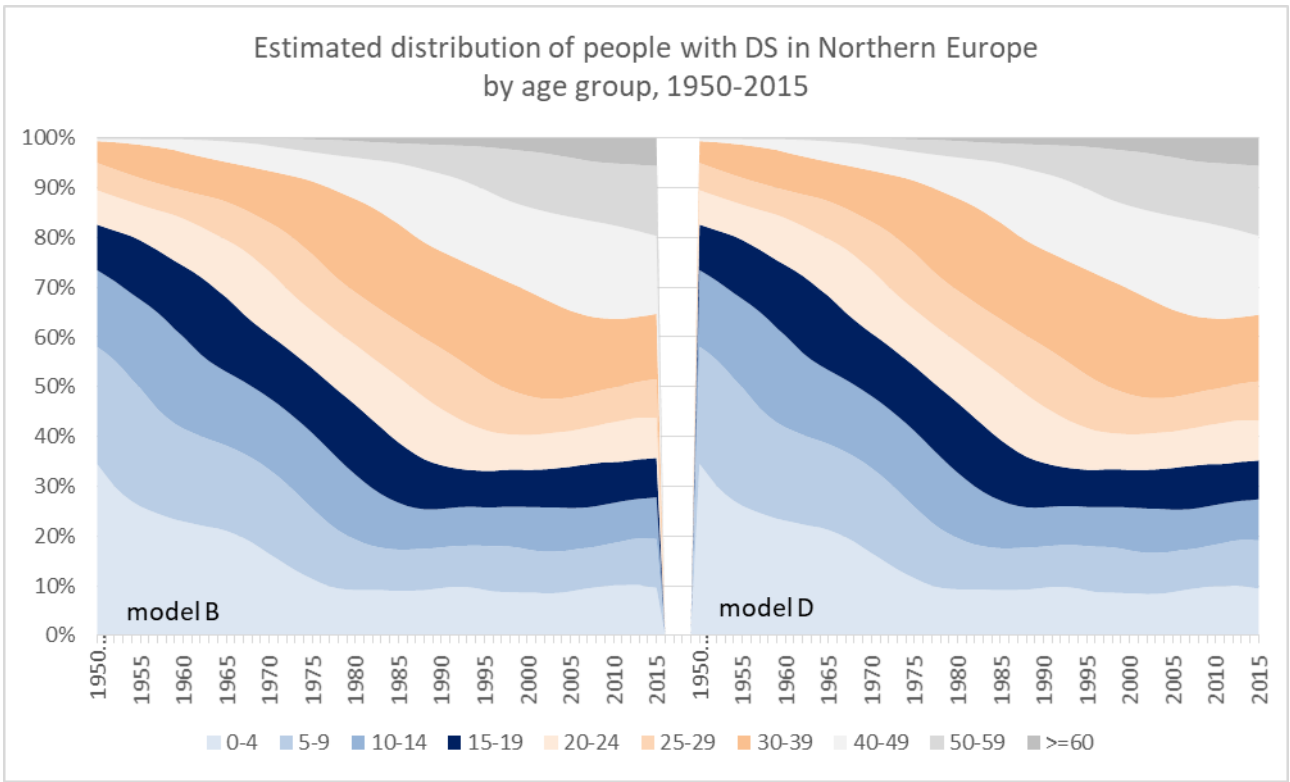


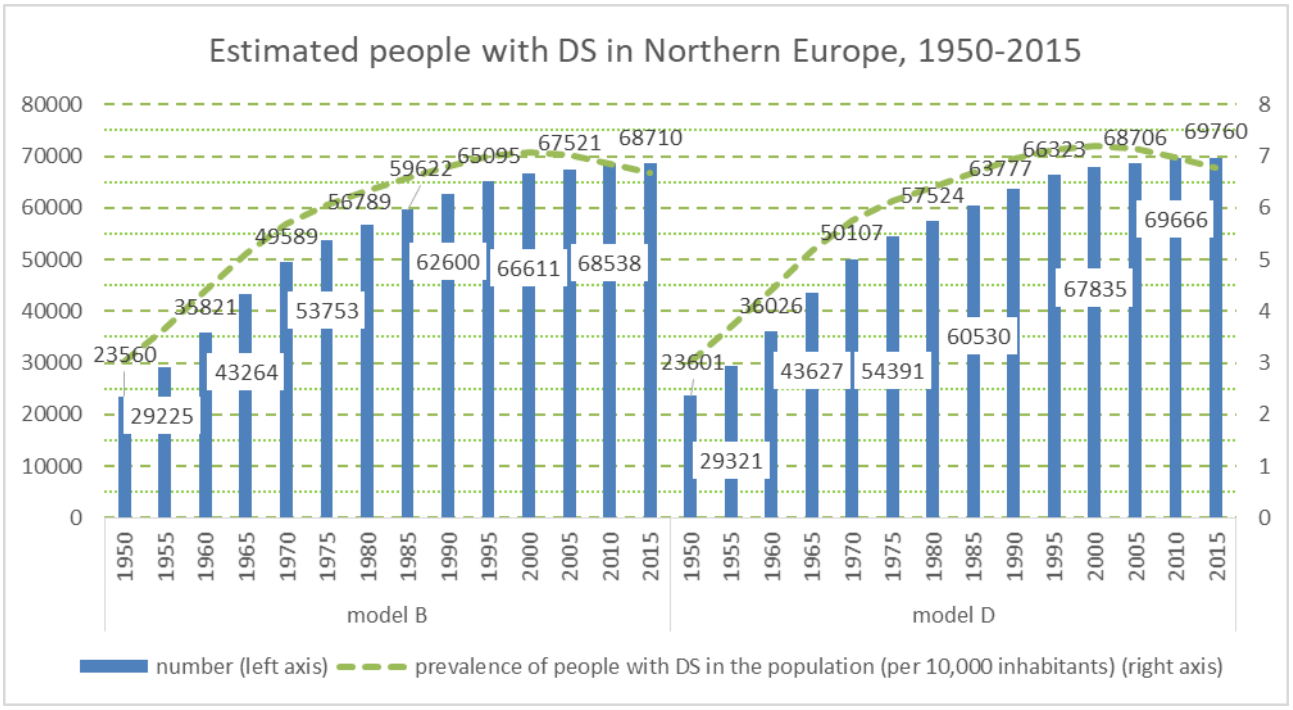


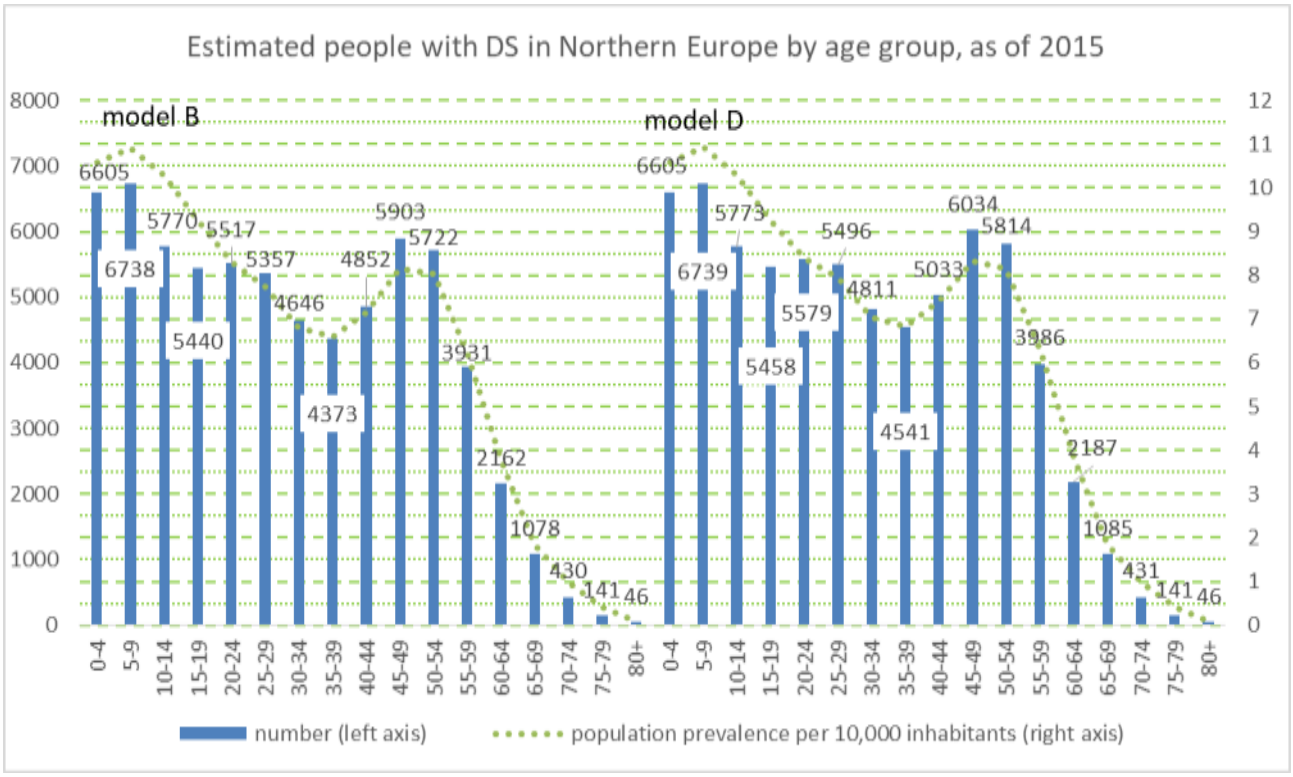


Model A projects 71,180 people with DS alive in 2015, which corresponds to a population prevalence of 6.9 people with DS per 10,000 inhabitants. However, Model A is unlikely, as it does not fit the data on age distribution of deaths with DS in former East bloc countries (see S5C). Model C predicts 70,689 people (6.9 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs below. As for Northern Europe, only the Baltic states were from the former East bloc; differences between the models are small.

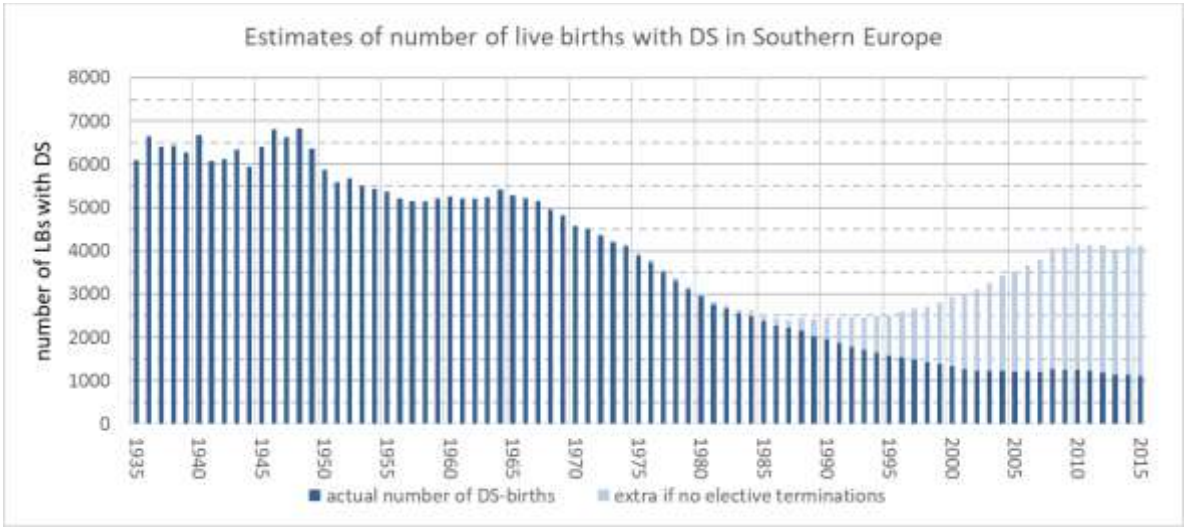


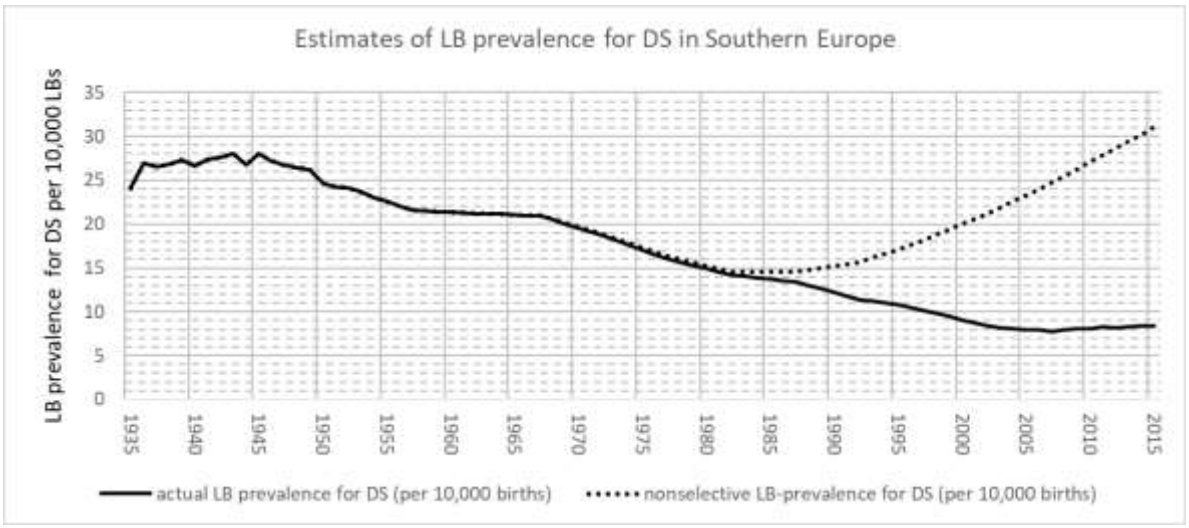


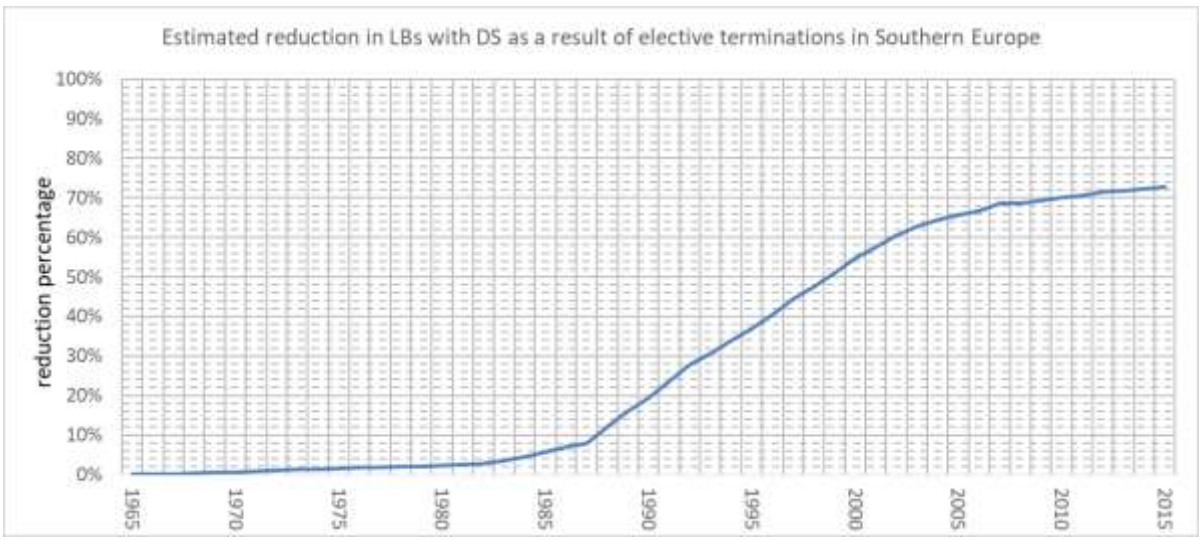

Estimated people with DS in Northern Europe, 1950-2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Northern Europe by age group, as of 2015
model B
model D
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

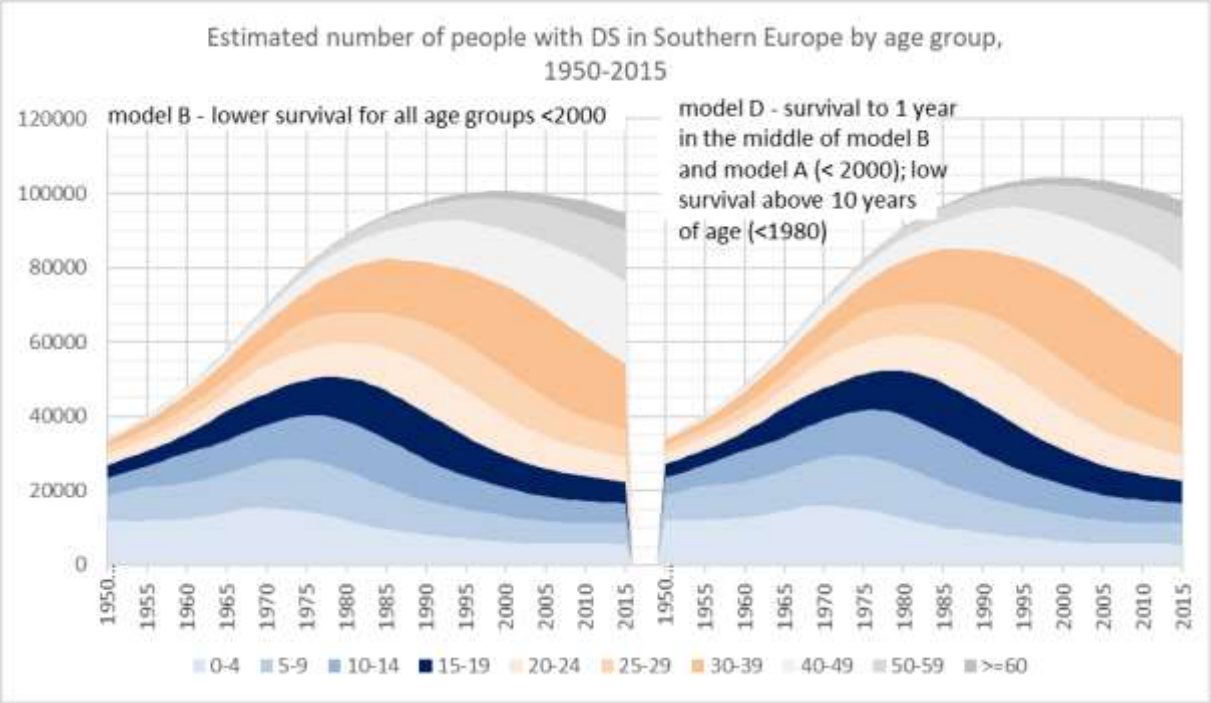
Southern Europe

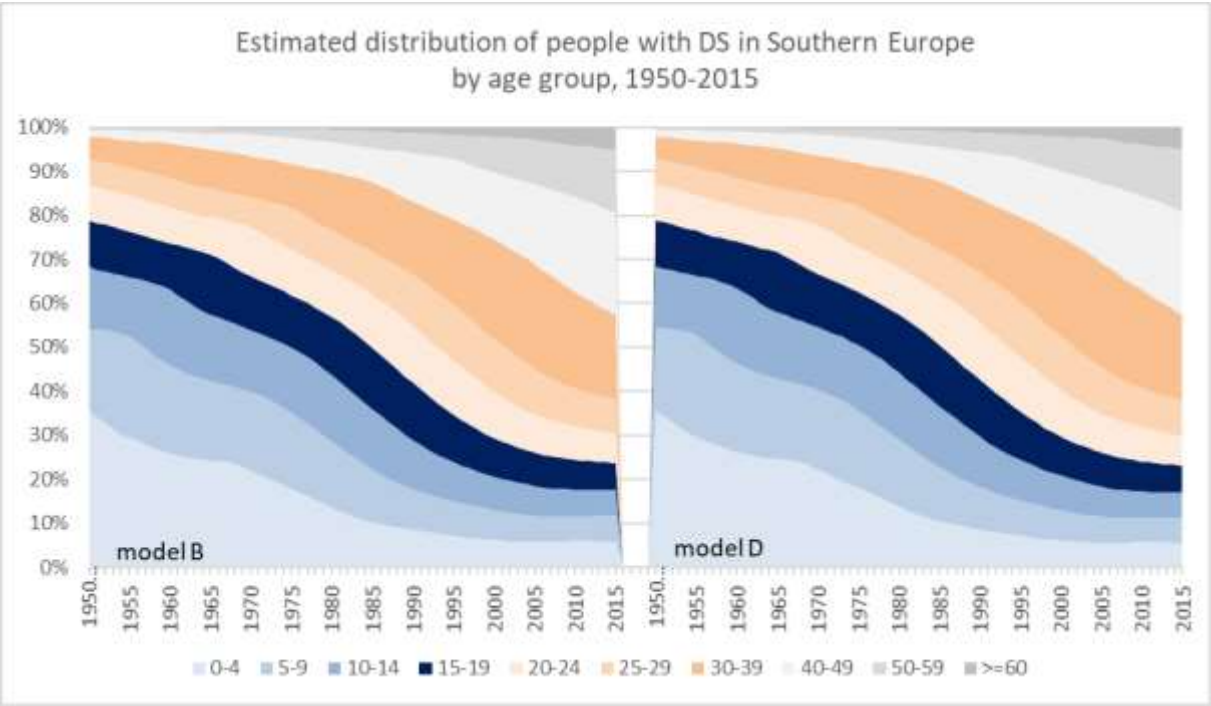


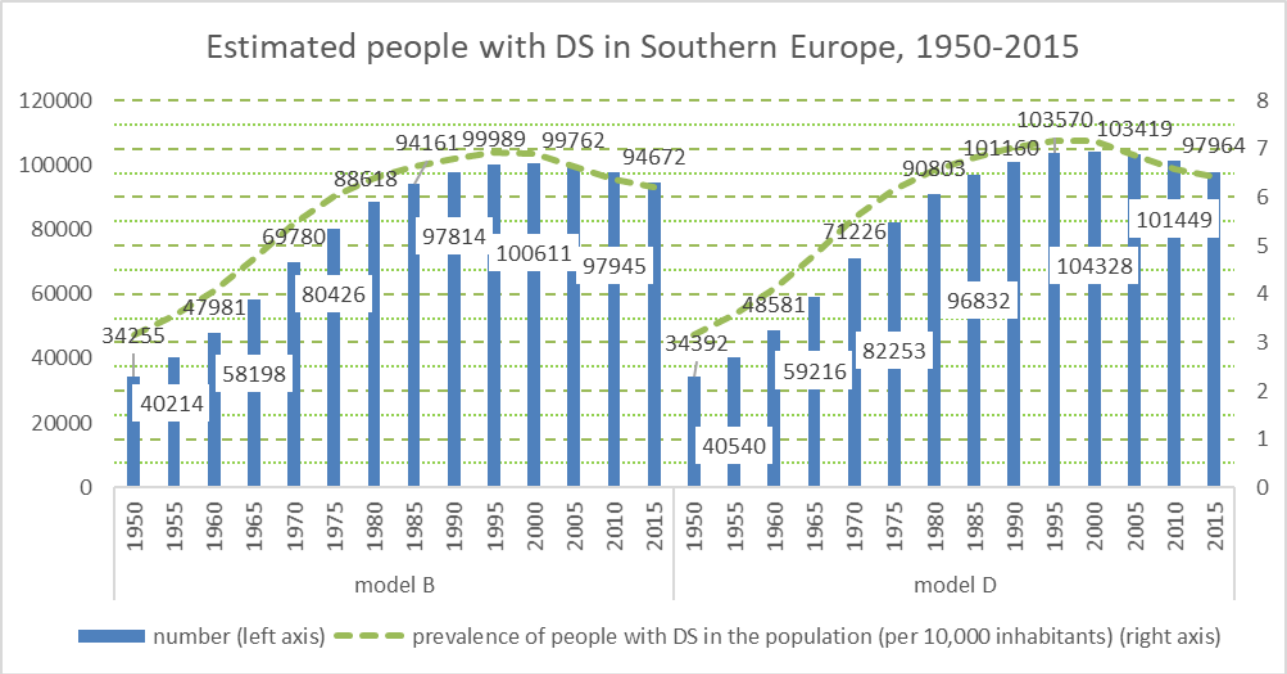


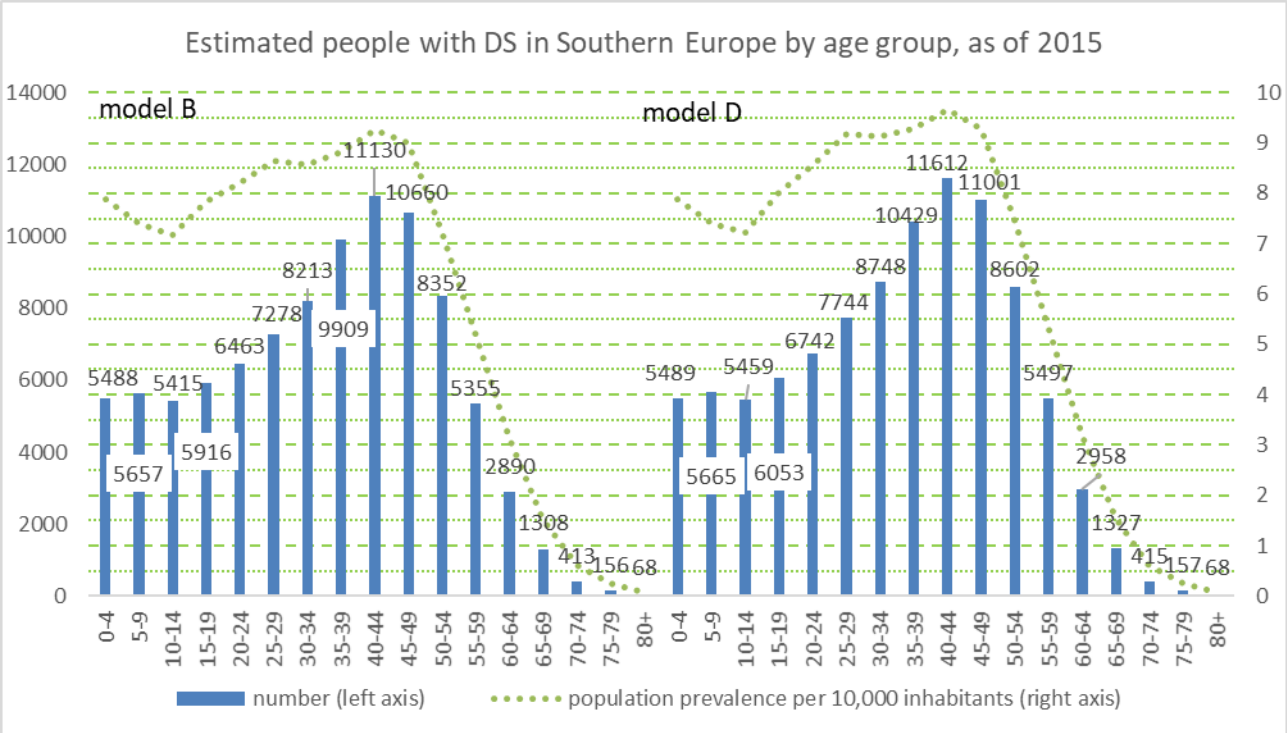


Model A projects 102,207 people with DS alive in 2015, which corresponds to a population prevalence of 6.7 people with DS per 10,000 inhabitants. However, Model A is unlikely, as it does not fit the data on age distribution of deaths with DS in former East bloc countries (see S5C). Model C predicts 101,265 people (6.5 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. As for Southern Europe, the majority of people with DS live in former West bloc countries; differences between the models are relatively small.

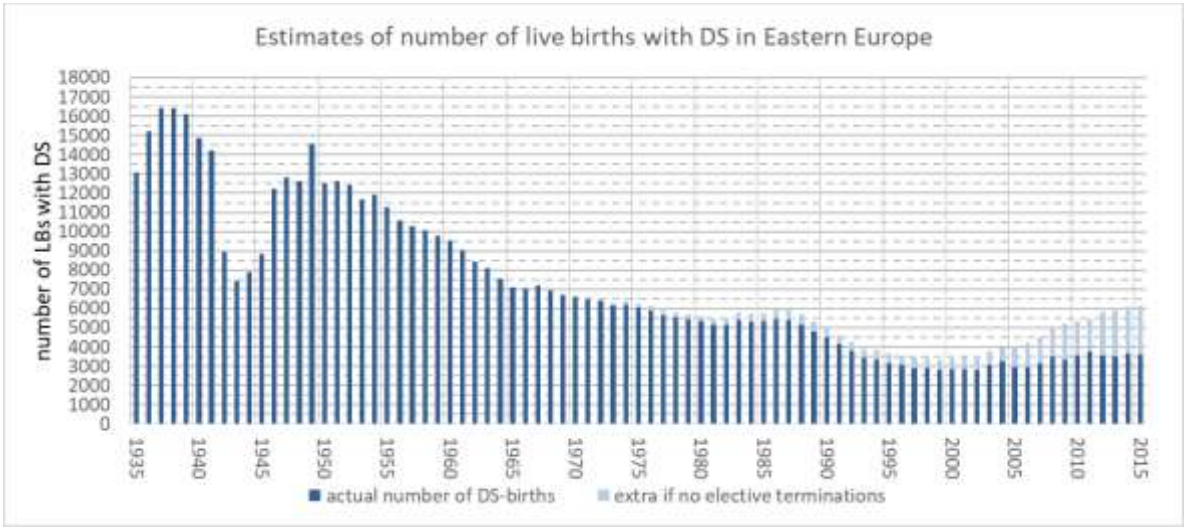


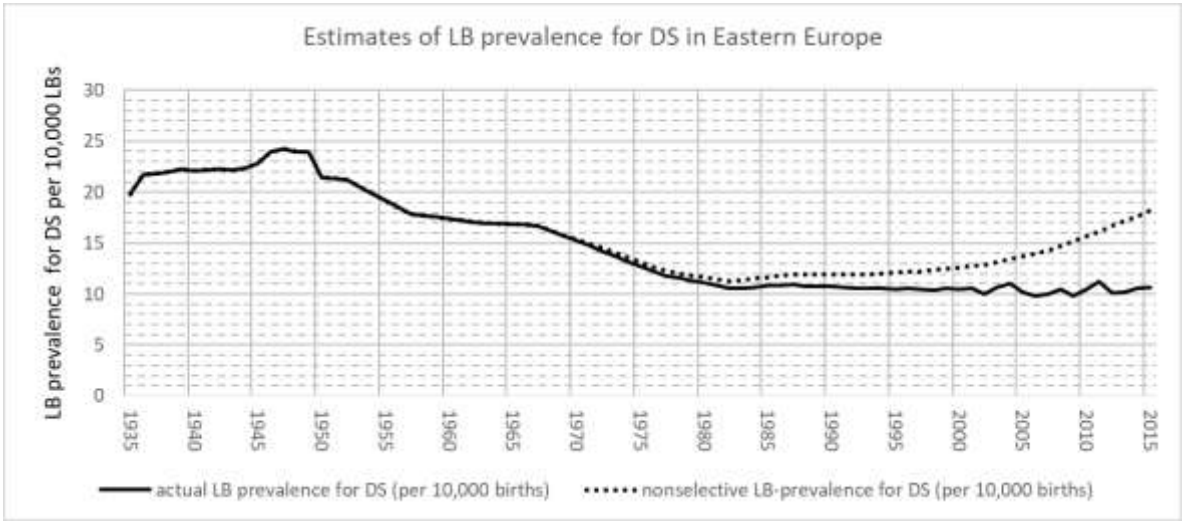


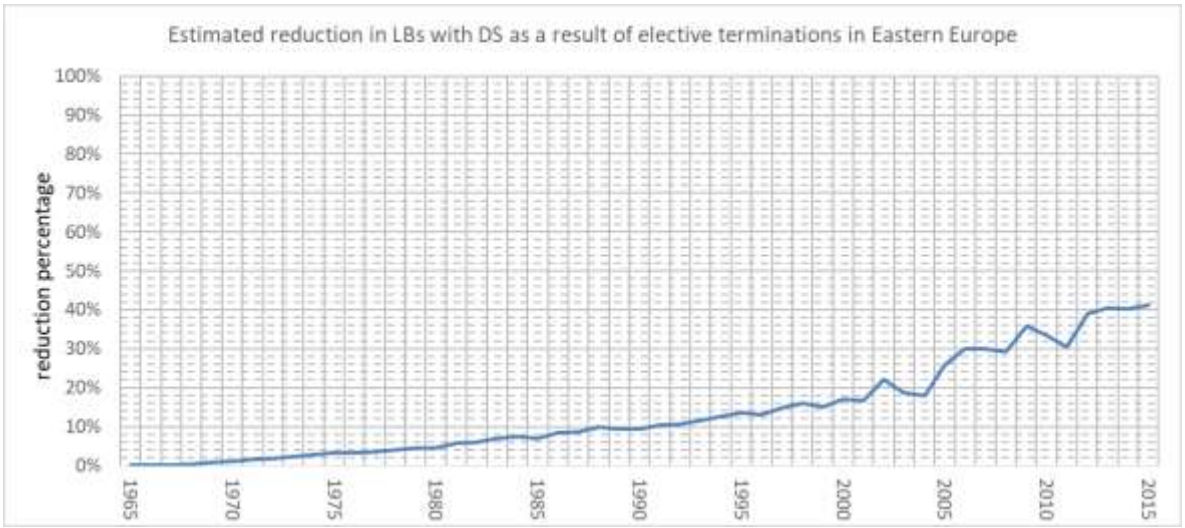

Estimated people with DS in Southern Europe, 1950-2015
120000
100000
80000
60000
40000
20000
0
8
7
6
5
4
3
2
1
0
34255
40214
47981
58198
69780
80426
88618
94161
99989
99762
94672
97814
100611
97945
34392
40540
48581
59216
71226
82253
90803
96832
101160
103570
103419
97964
101449
104328
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in Southern Europe by age group, as of 2015
14000
12000
10000
8000
6000
4000
2000
0
10
9
8
7
6
5
4
3
2
1
0
model B
model D
5488
5657
5415
5916
6463
7278
8213
9909
11130
10660
8352
5355
2890
1308
413
156
68
5489
5665
5459
6053
6742
7744
8748
10429
11612
11001
8602
5497
2958
1327
415
157
68
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

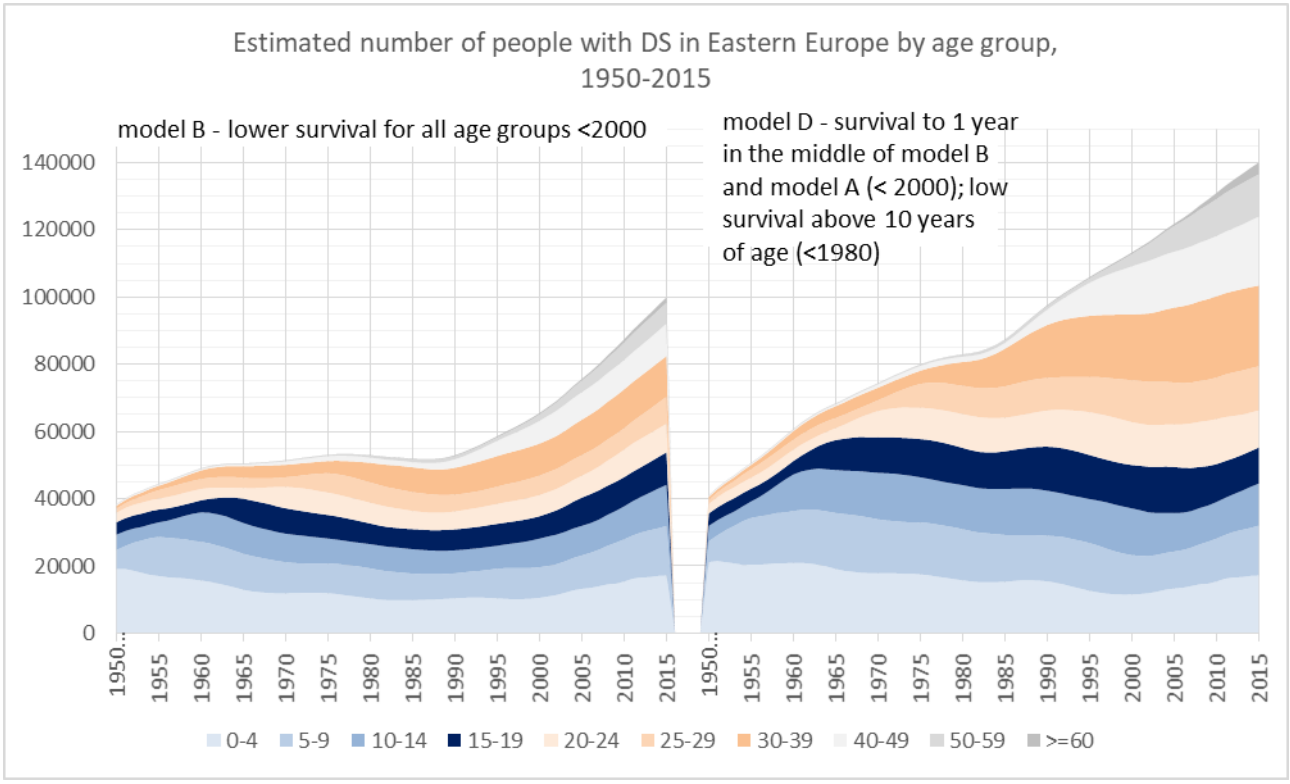
Eastern Europe

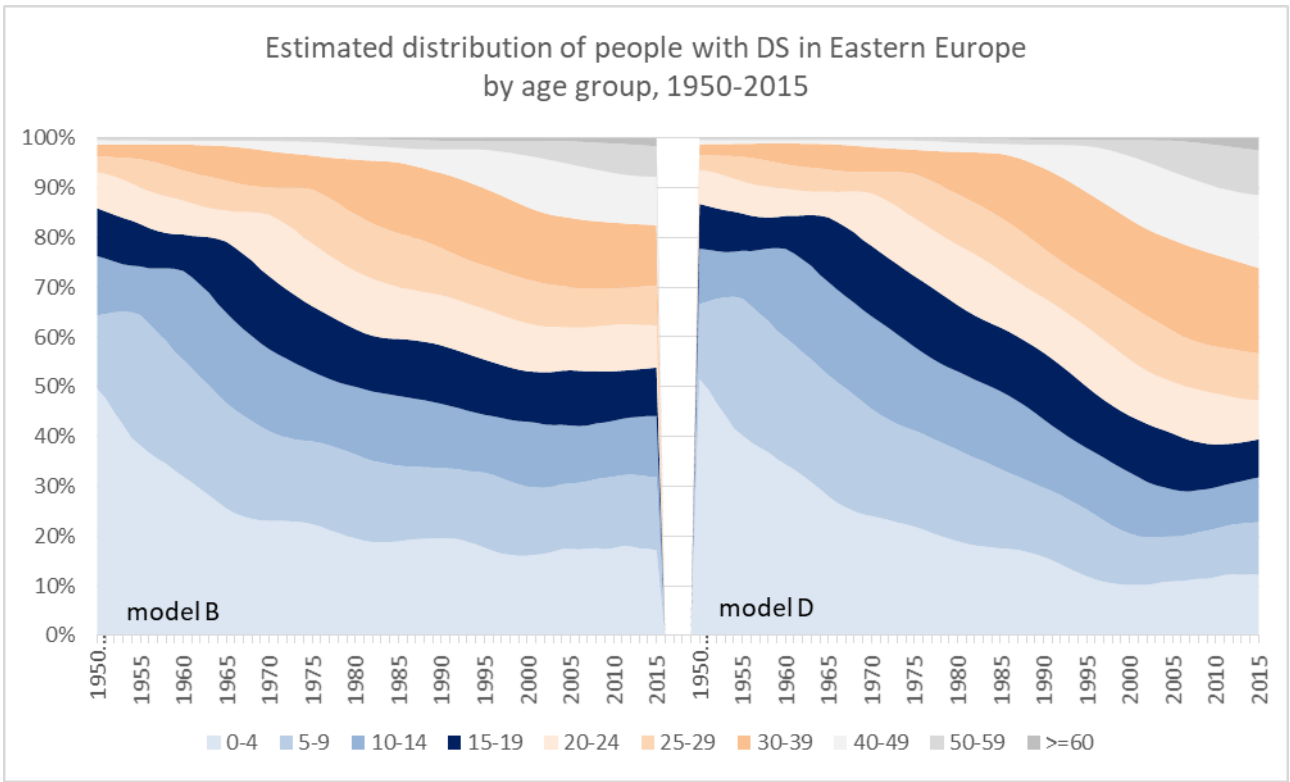


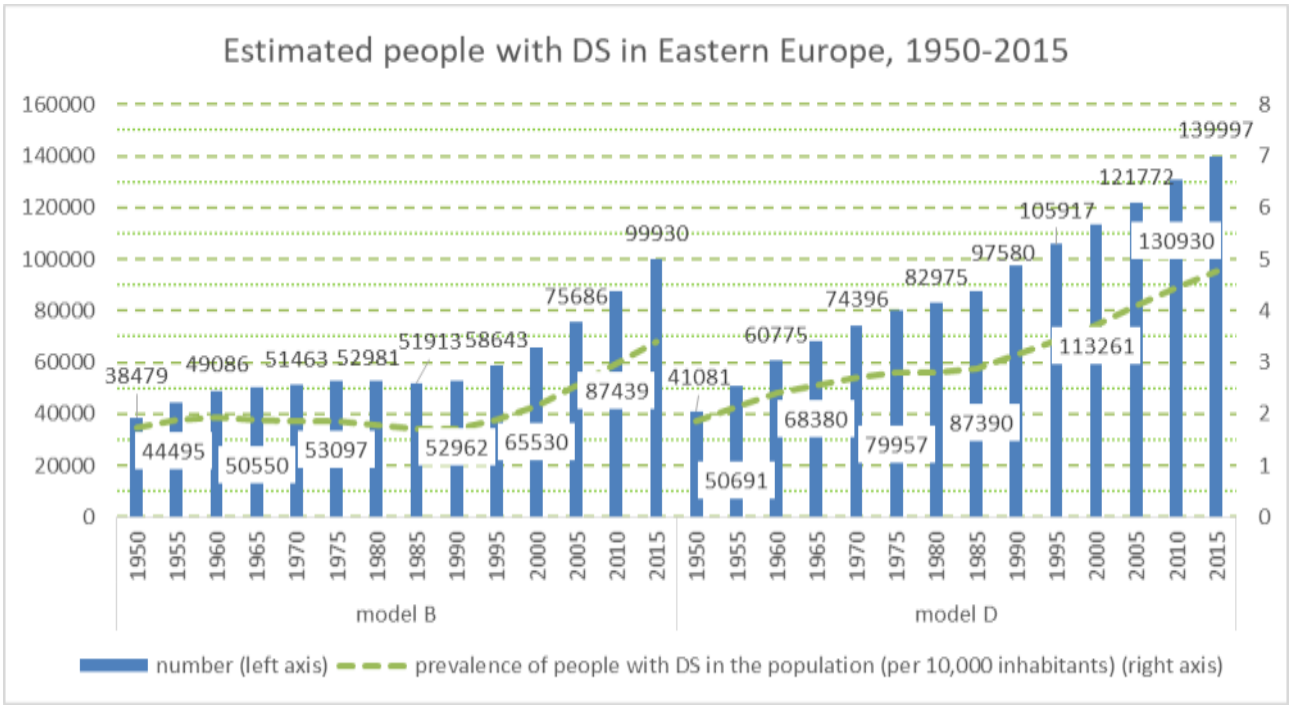


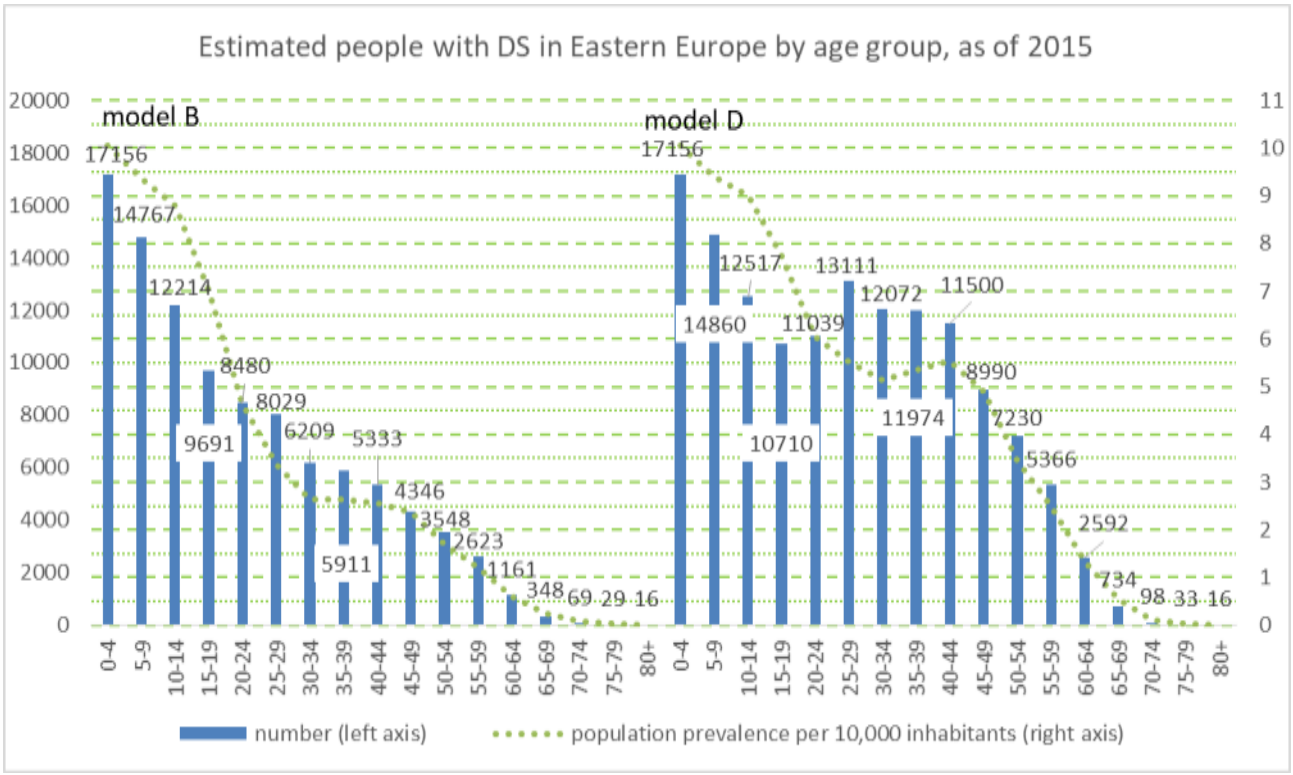


Model A projects 196,293 people with DS alive in 2015, which corresponds to a population prevalence of 6.7 people with DS per 10,000 inhabitants. However, Model A is unlikely, as it does not fit the data on age distribution of deaths with DS in former East bloc countries (see S5C). Model C predicts 176,791 people (6.0 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs. As Eastern Europe consists entirely of former East bloc countries, differences between the models are large.

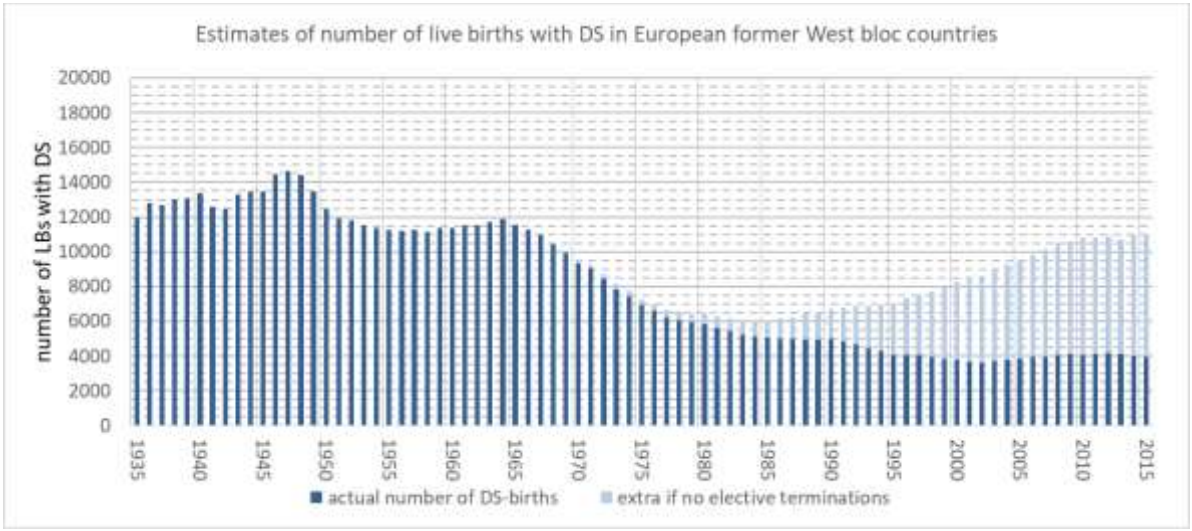


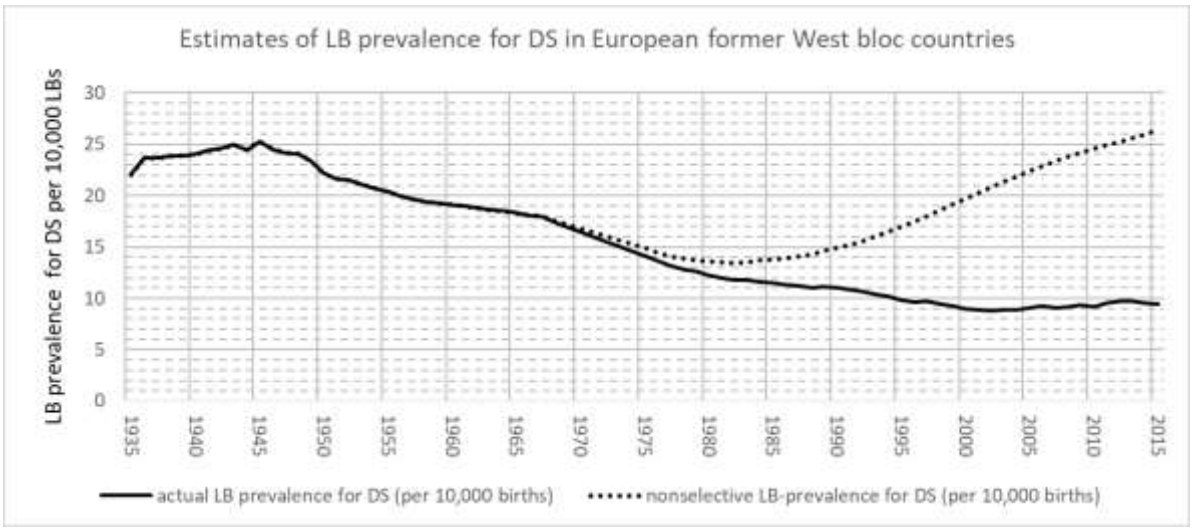


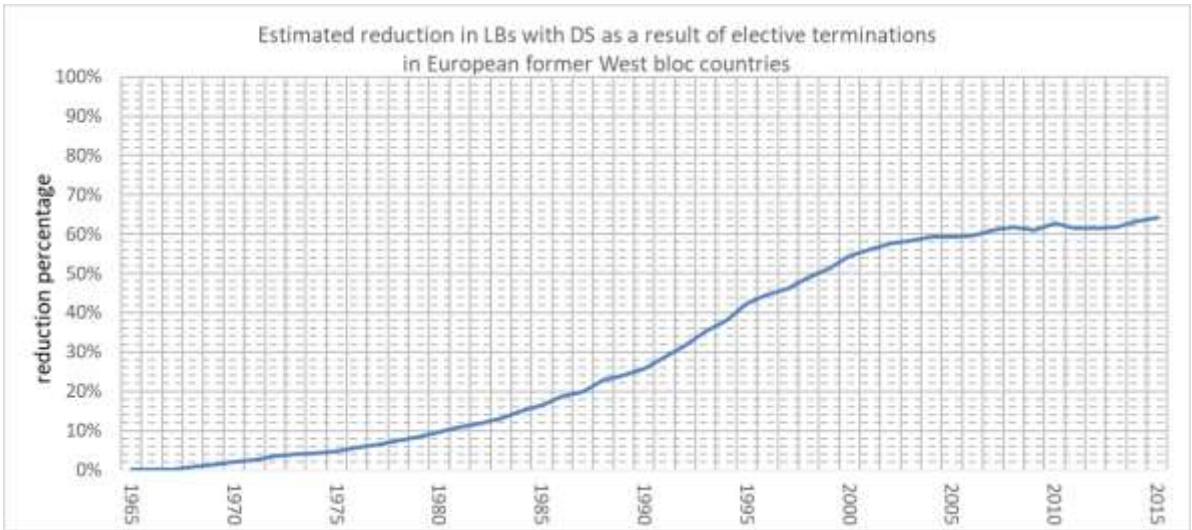

Estimated people with DS in Eastern Europe, 1950-2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

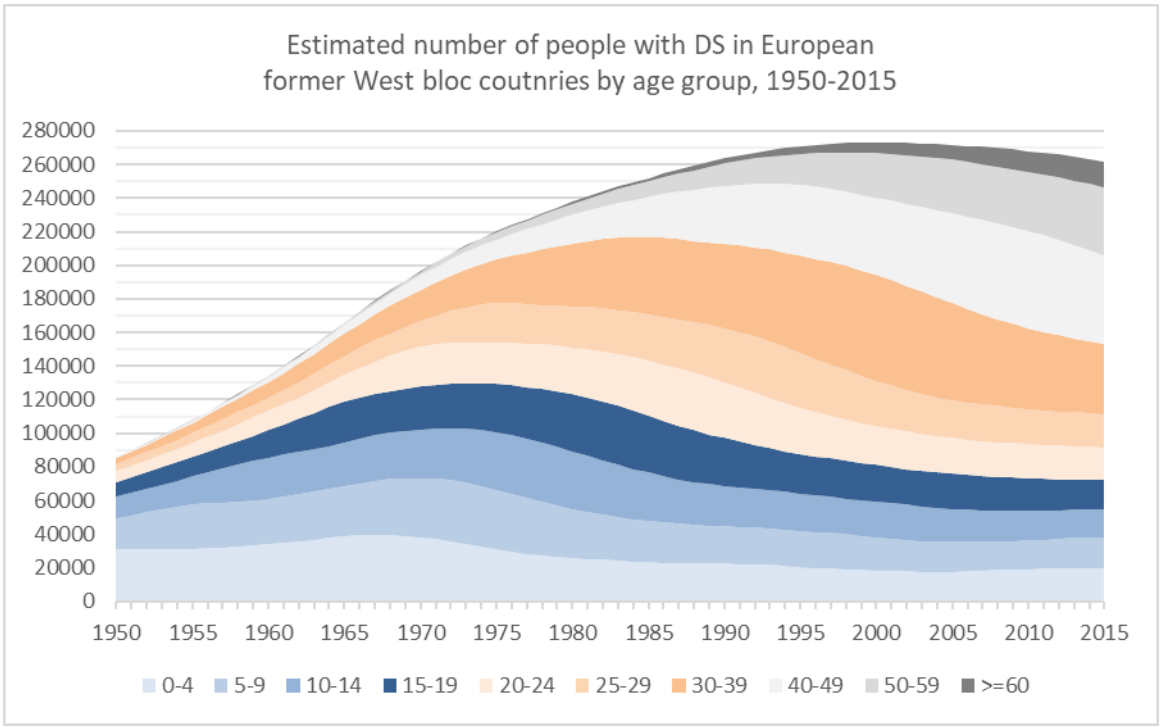

Estimated people with DS in Eastern Europe by age group, as of 2015
model B
model D
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

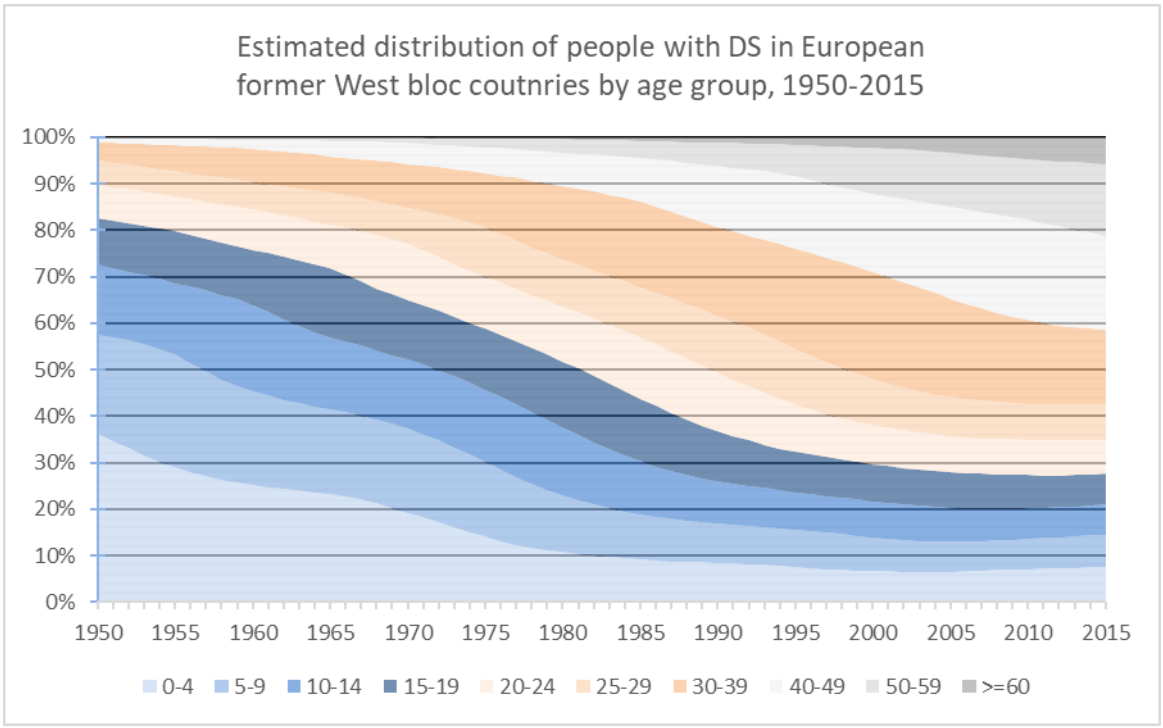
Europe: former West bloc countries

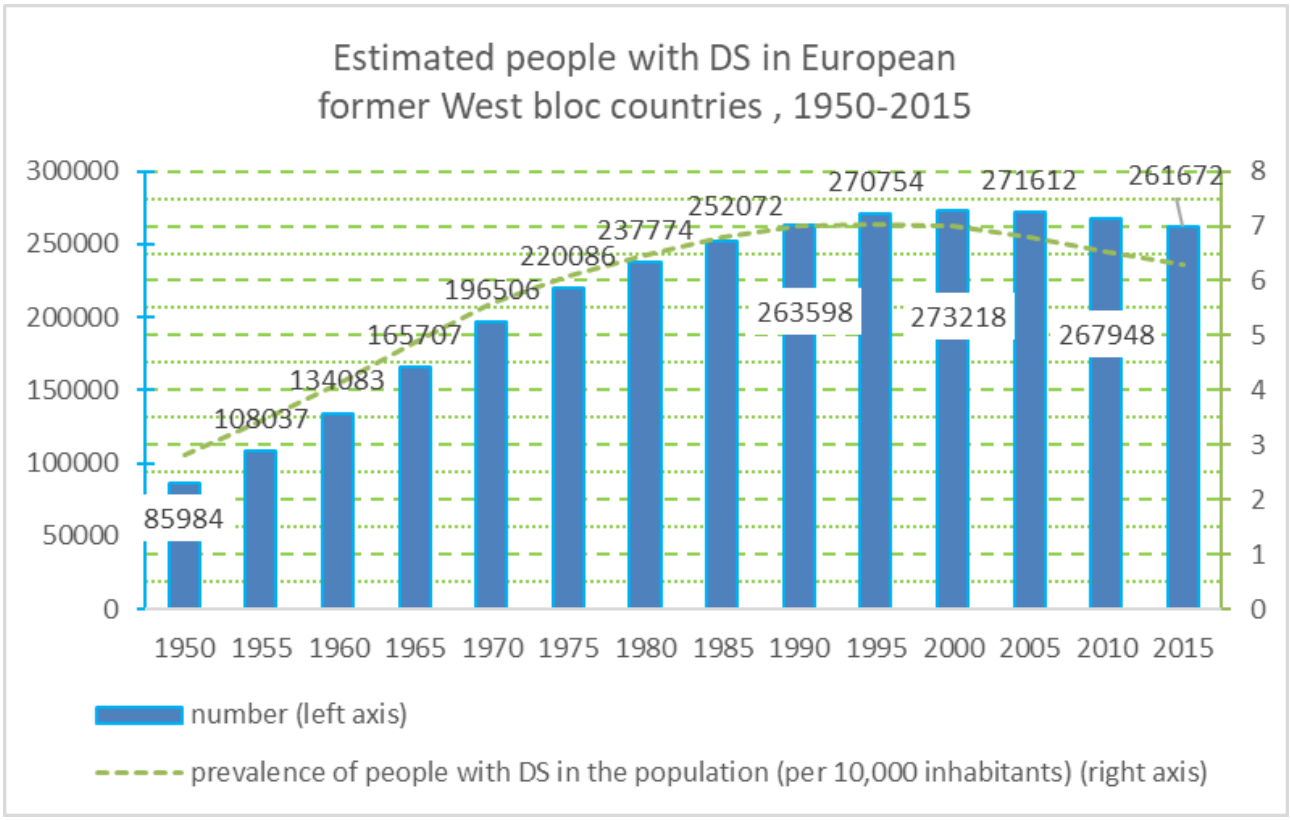


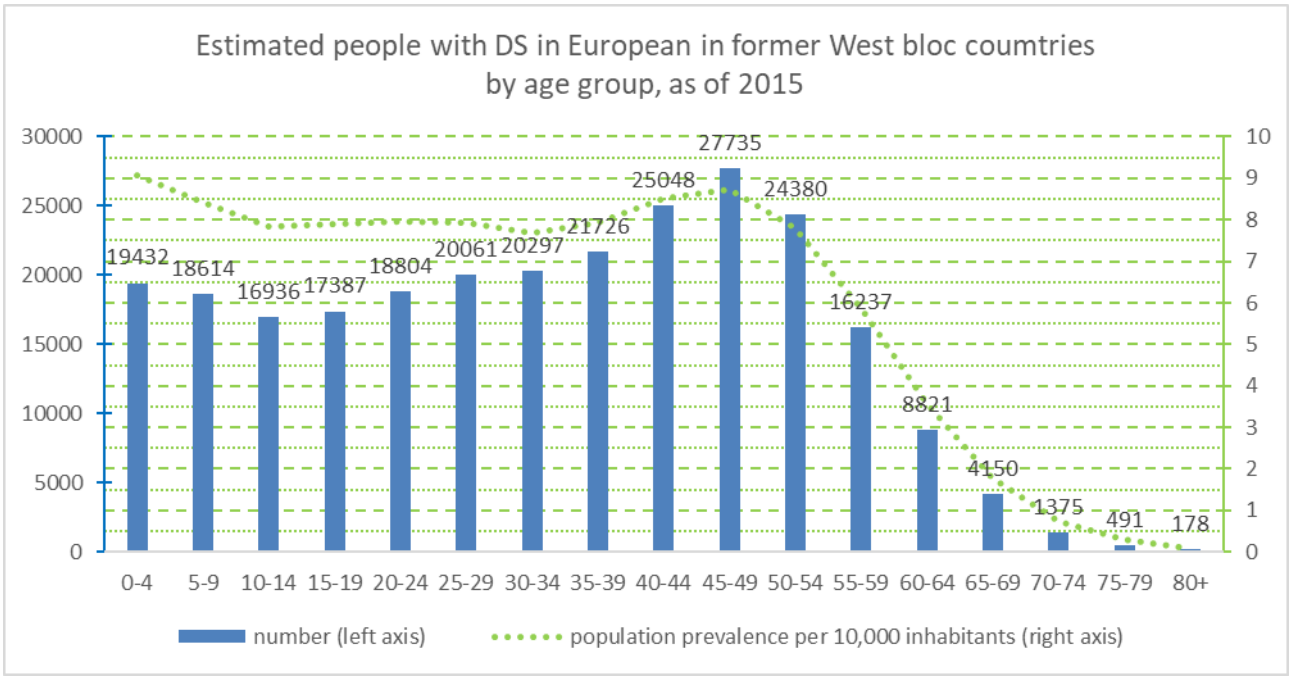




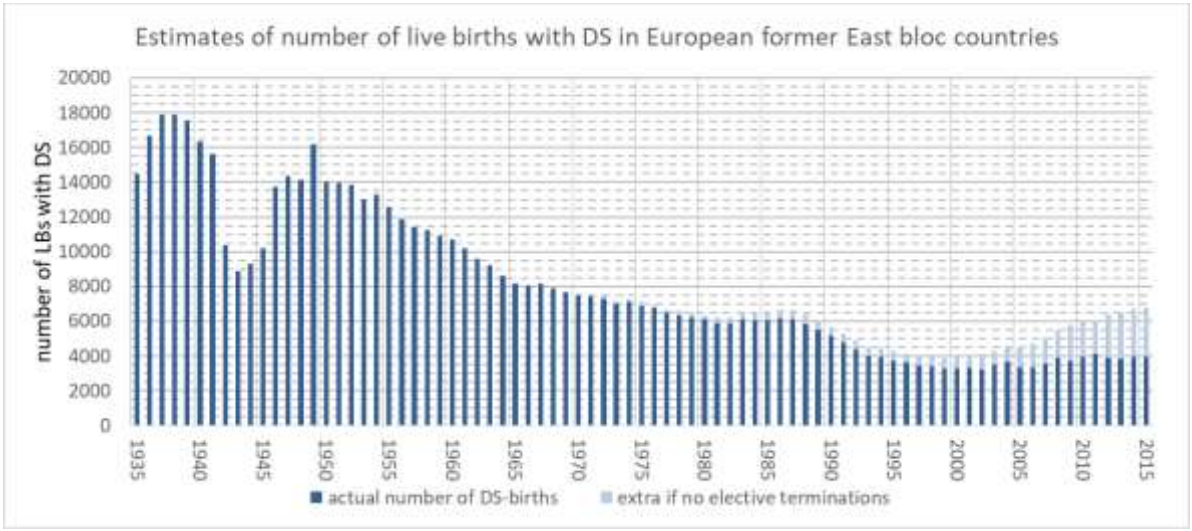

Estimated number of people with DS in European former West bloc coutnries by age group, 1950-2015
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

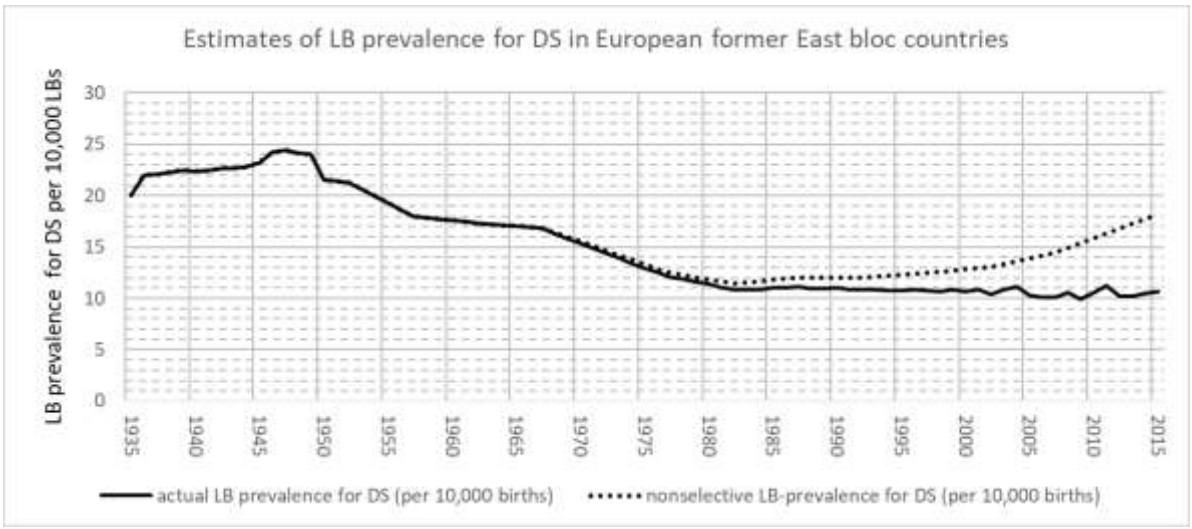

Estimated distribution of people with DS in European former West bloc coutnries by age group, 1950-2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
0-4 5-9 10-14 15-19 20-24 25-29 30-39 40-49 50-59 >=60

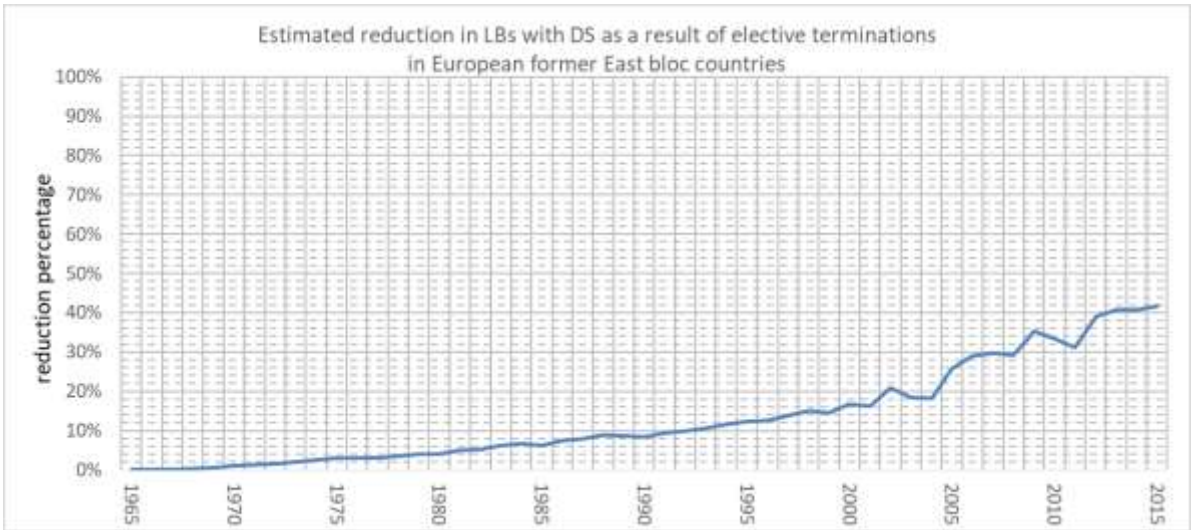

Estimated people with DS in European former West bloc countries , 1950-2015
300000
250000
200000
150000
100000
50000
0
8
7
6
5
4
3
2
1
0
85984
108037
134083
165707
196506
220086
237774
252072
263598
270754
273218
271612
267948
261672
1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in European in former West bloc coumtries by age group, as of 2015
30000
25000
20000
15000
10000
5000
0
10
9
8
7
6
5
4
3
2
1
0
19432
18614
16936
17387
18804
20061
20297
21726
25048
27735
24380
16237
8821
4150
1375
491
178
0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

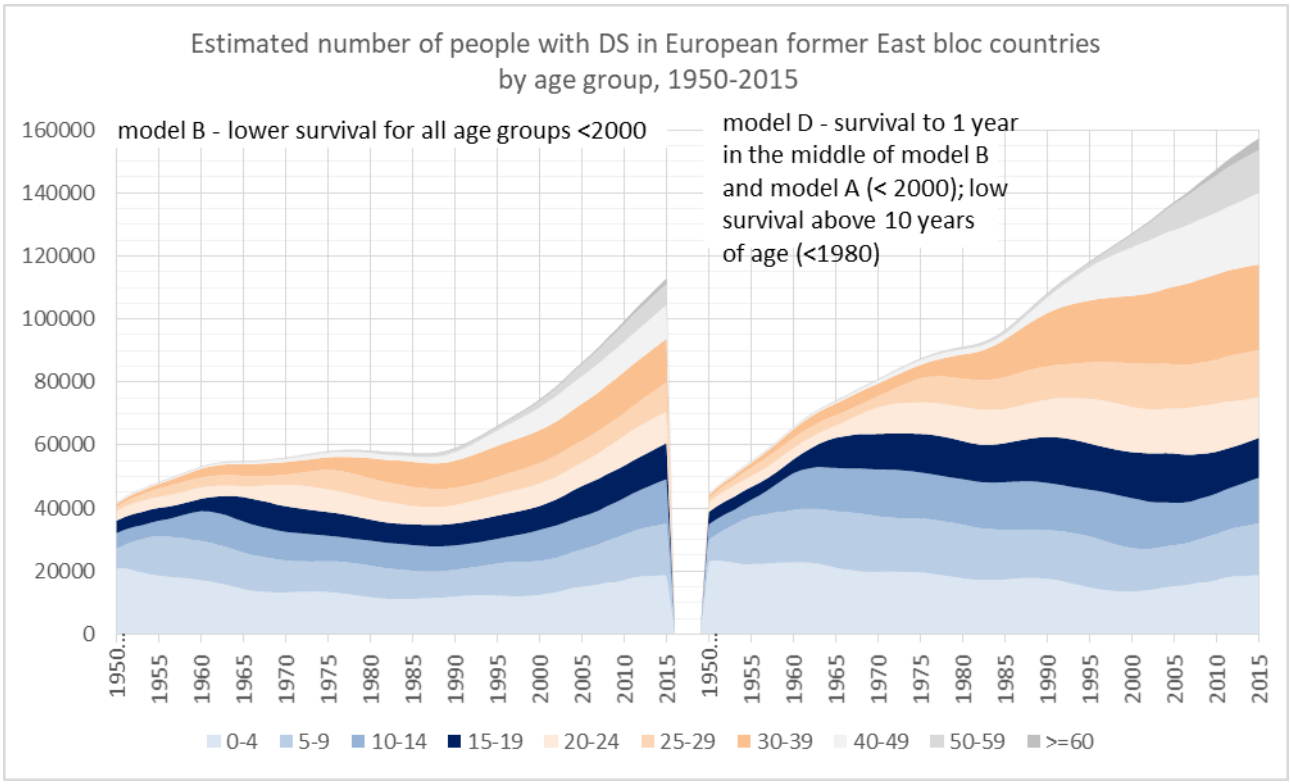
Europe: former East bloc countries

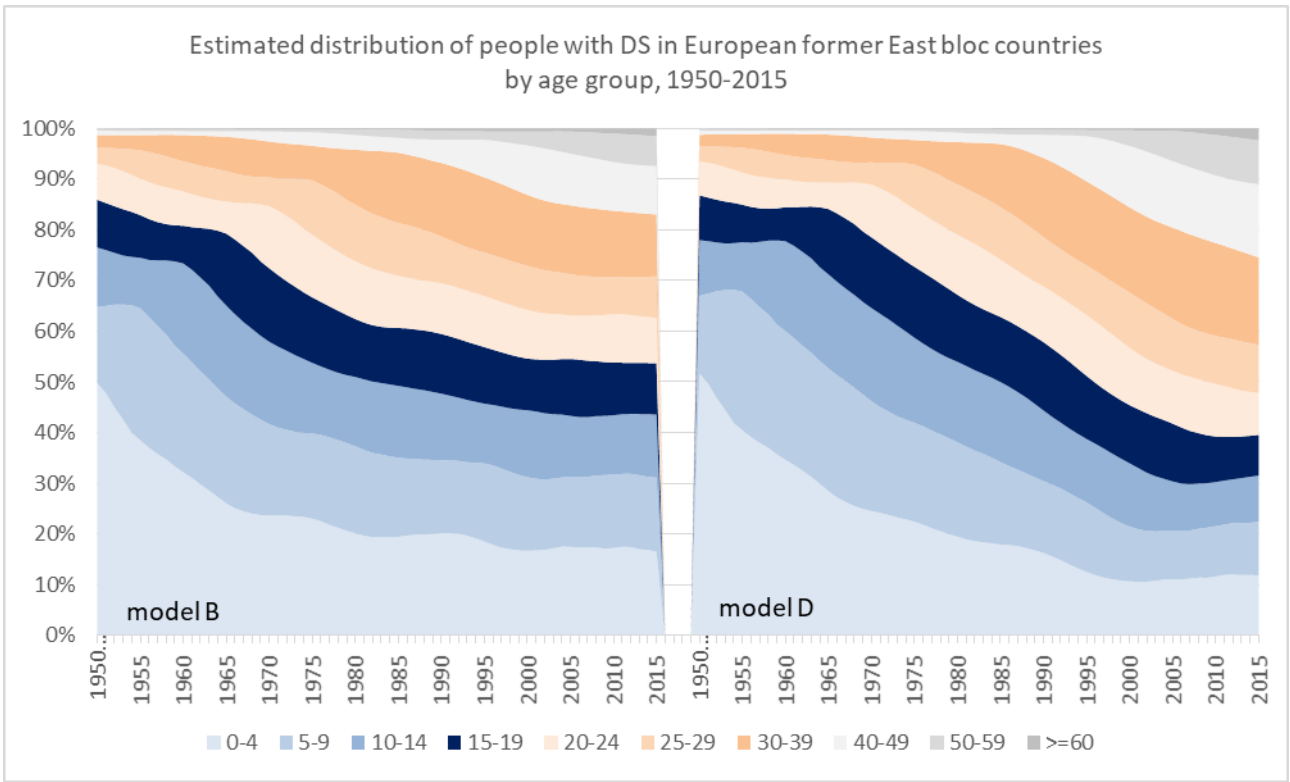


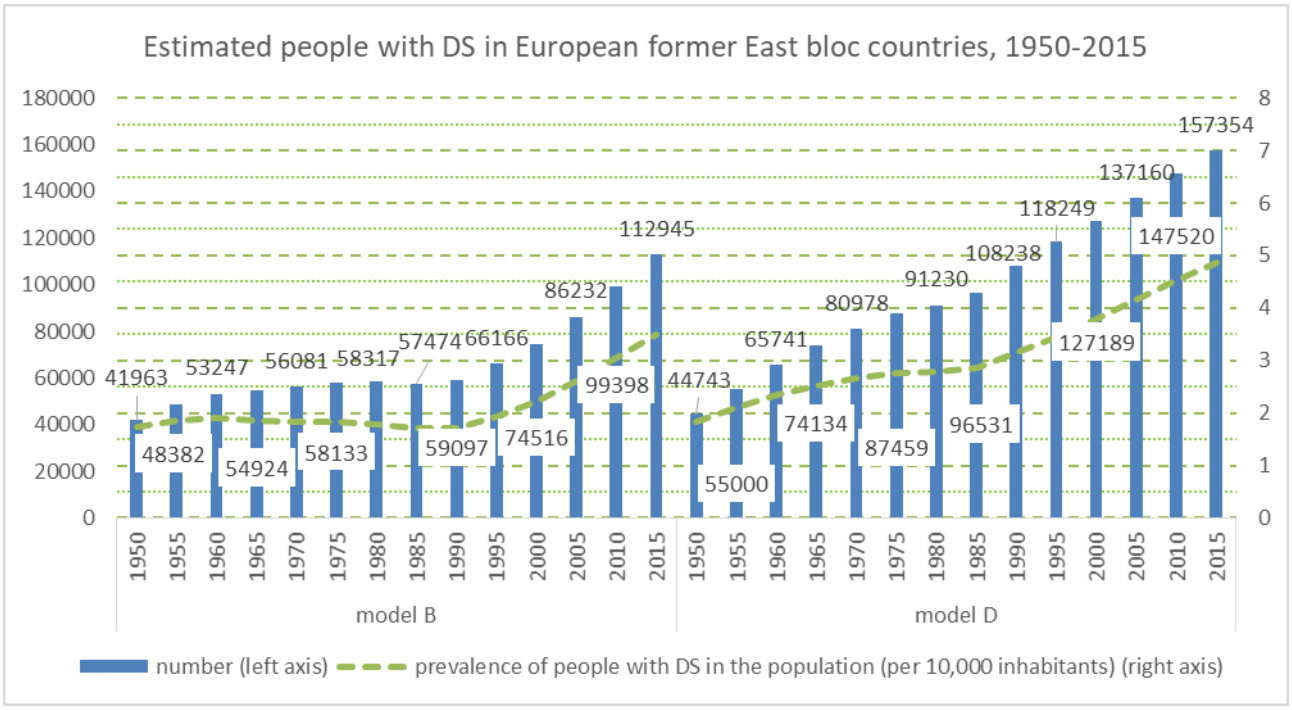


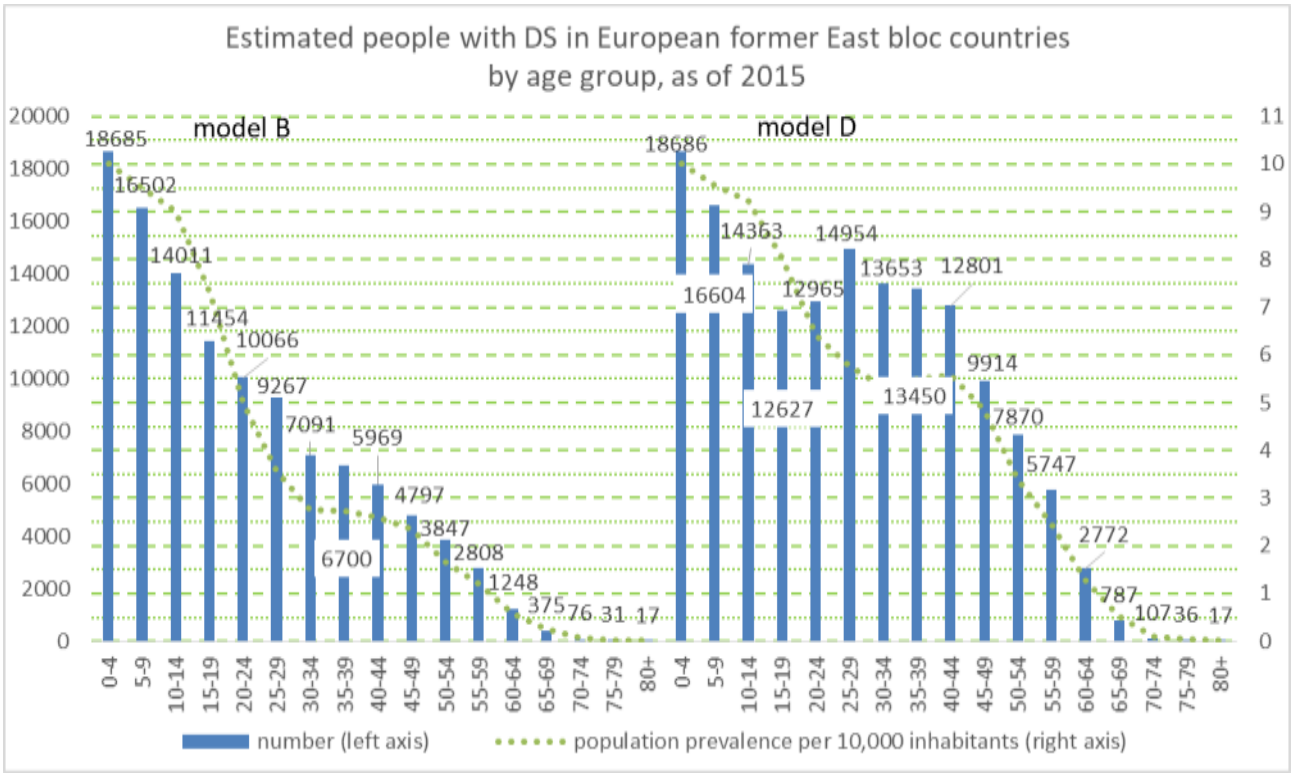


Model A projects 219,313 people with DS alive in 2015, which corresponds to a population prevalence of 6.8 people with DS per 10,000 inhabitants. However, Model A is unlikely, as it does not fit the data on age distribution of deaths with DS in former East bloc countries (see S5C). Model C predicts 198,378 people (6.1 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs.

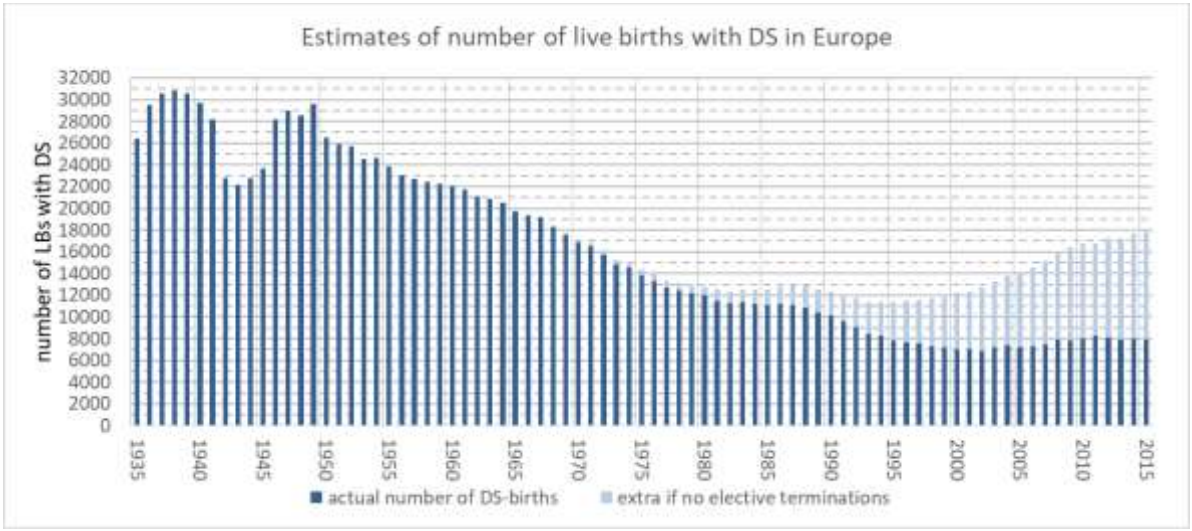


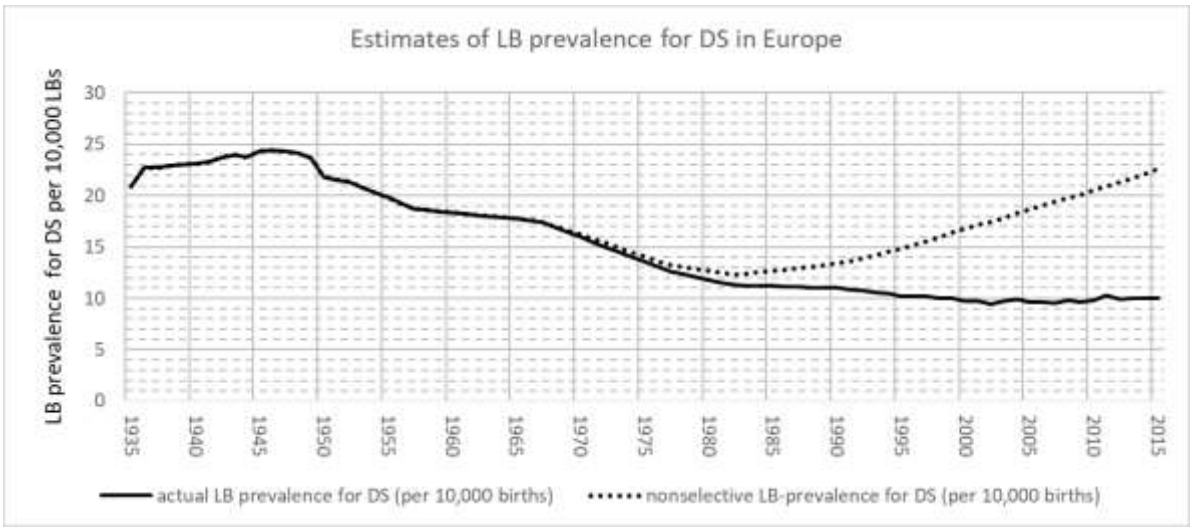


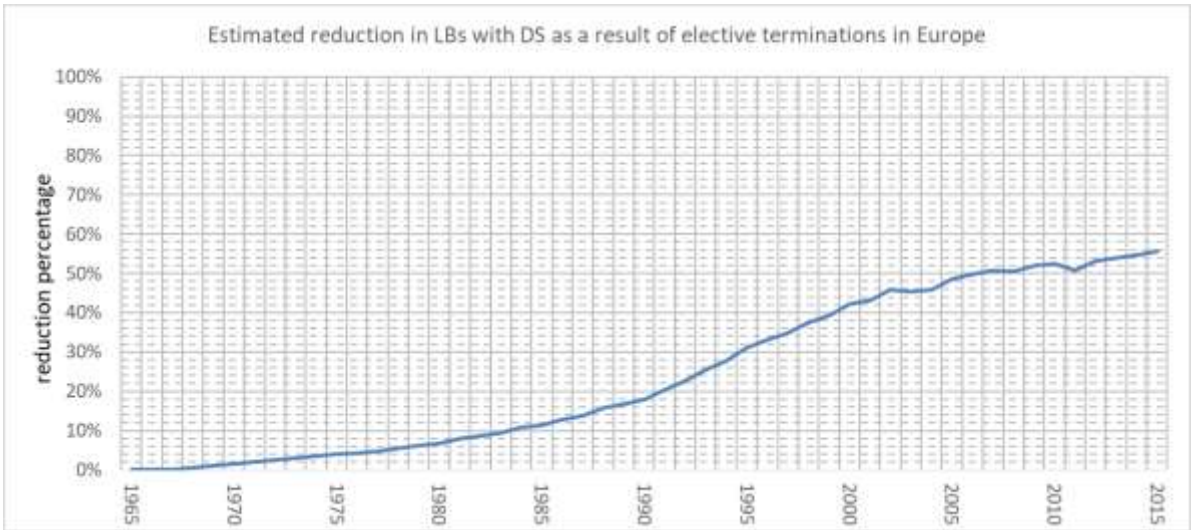

Estimated people with DS in European former East bloc countries, 1950-2015
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
8
7
6
5
4
3
2
1
0
41963
48382
53247
54924
56081
58133
58317
59097
57474
66166
74516
86232
99398
112945
44743
55000
65741
74134
80978
87459
91230
96531
108238
118249
127189
137160
147520
157354
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)


Estimated people with DS in European former East bloc countries
by age group, as of 2015
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
11
10
9
8
7
6
5
4
3
2
1
0
model B
model D
18685
16502
14011
11454
10066
9267
7091
6700
5969
4797
3847
2808
1248
375
76
31
17
18686
16604
14363
12627
12965
14954
13653
13450
12801
9914
7870
5747
2772
787
107
36
17
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

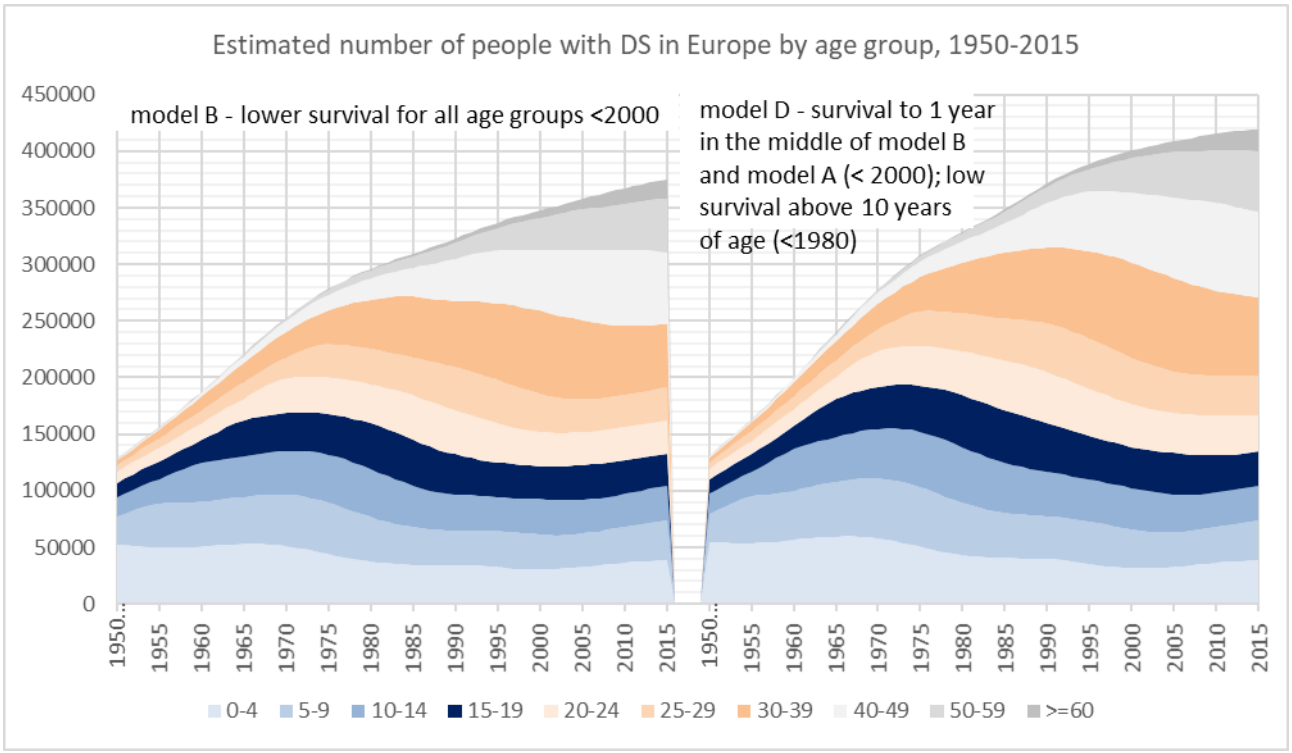
Europe: Total

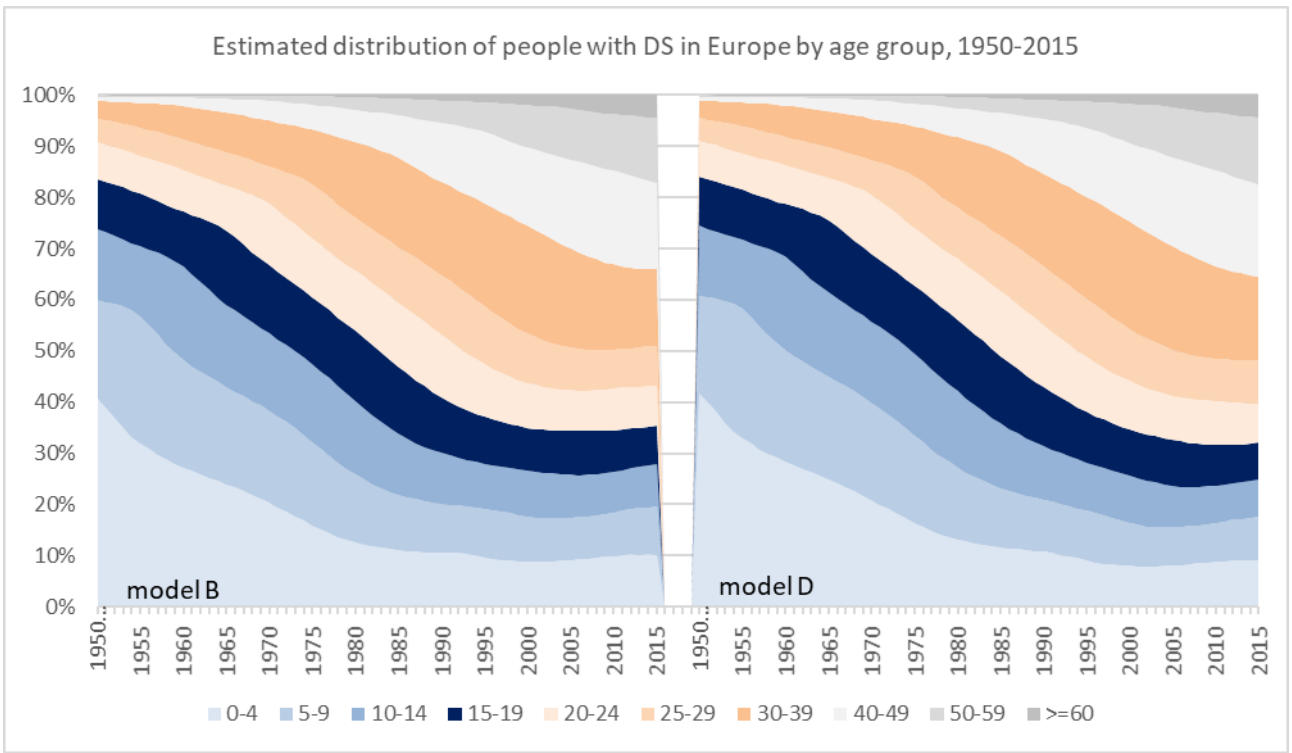


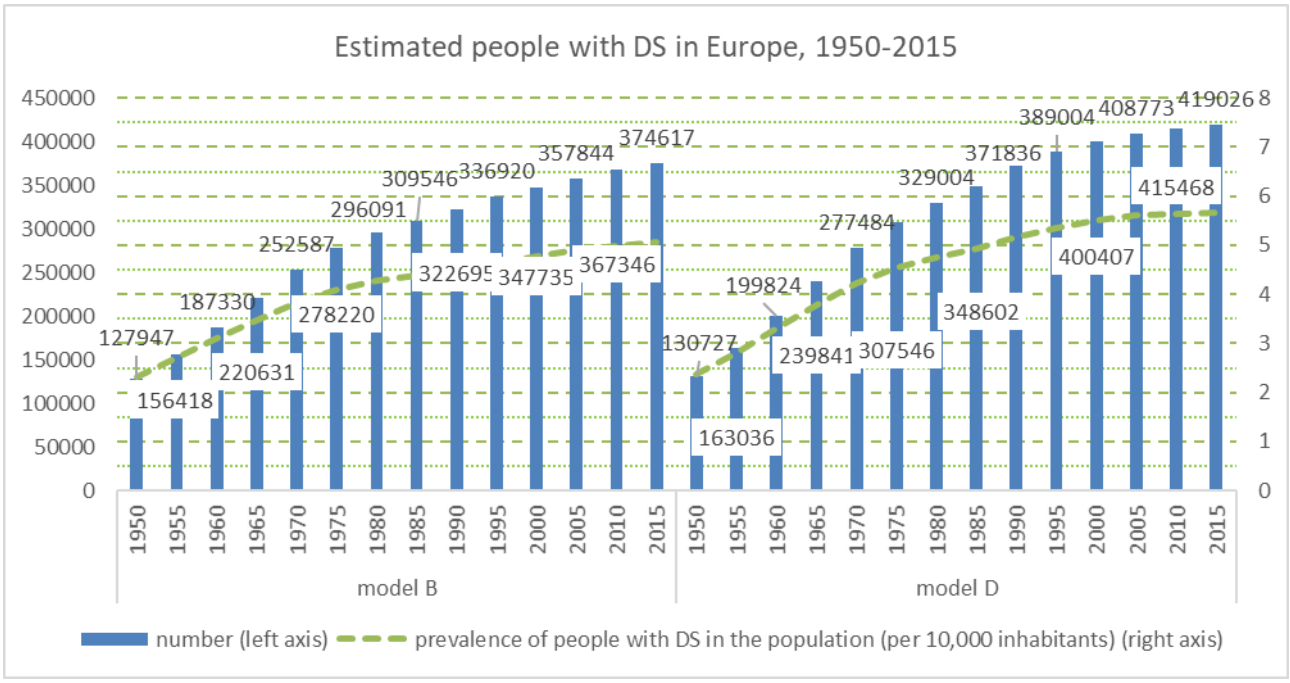


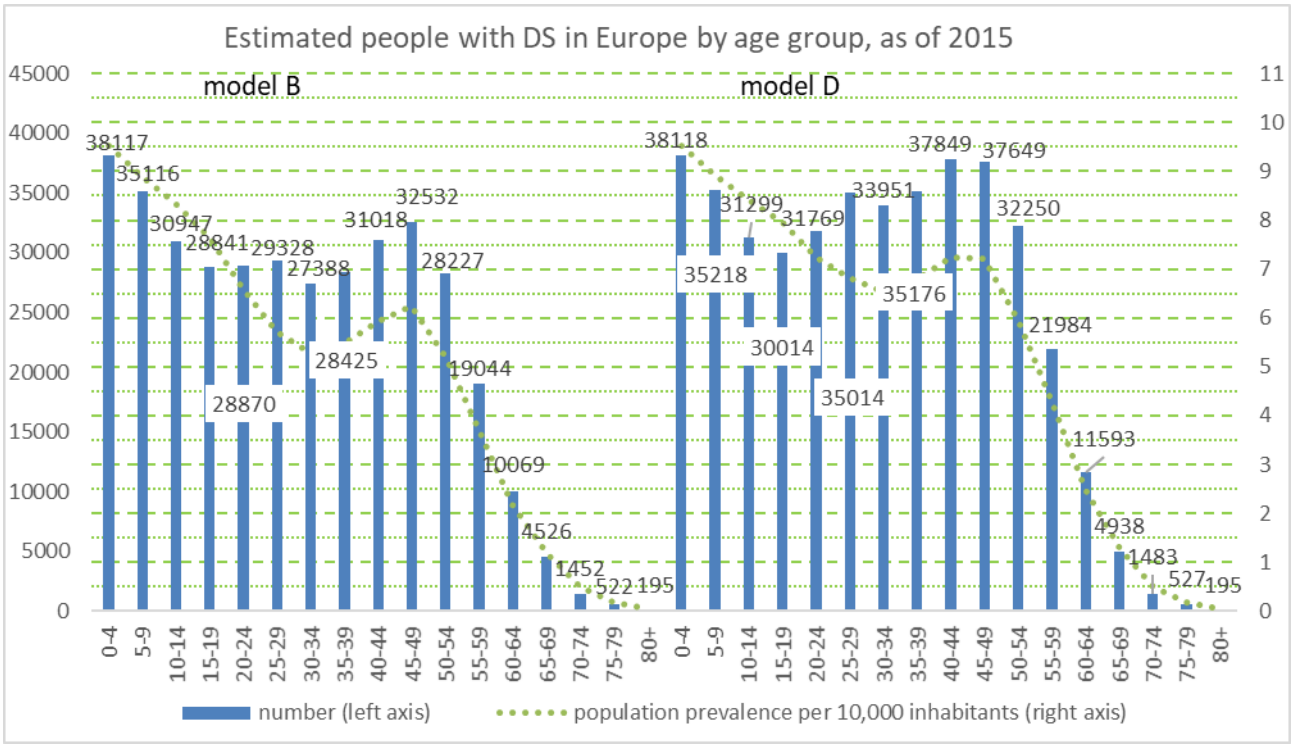


Model A projects 480,985 people with DS alive in 2015, which corresponds to a population prevalence of 6.5 people with DS per 10,000 inhabitants. However, Model A is unlikely, as it does not fit the data on age distribution of deaths with DS in former East bloc countries (see S5C). Model C predicts 460,050 people (6.2 per 10,000); however, we deem a model in which only survival above 10 years of age is lowered as not credible. Model B and Model D are depicted in the graphs.



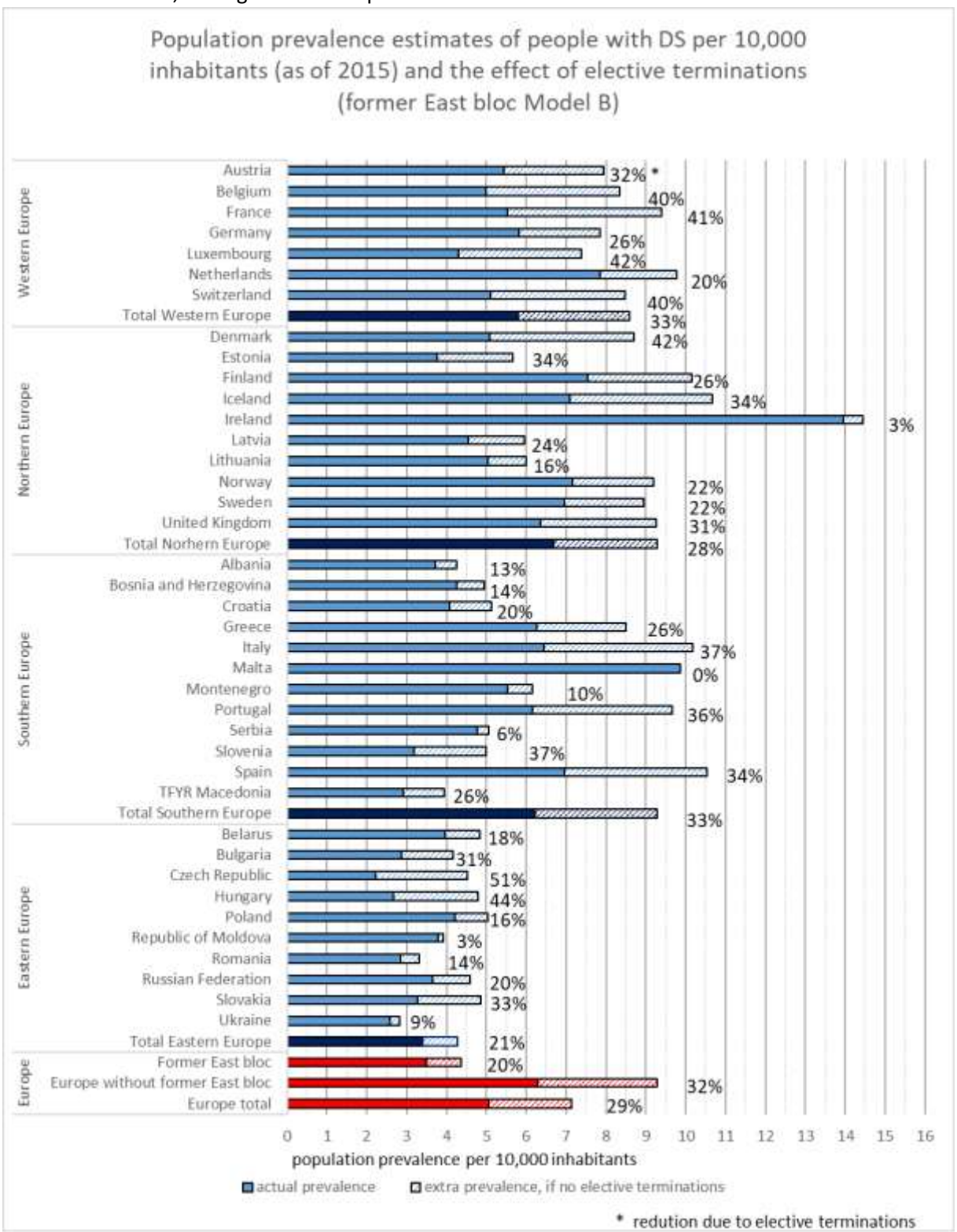



Estimated people with DS in Europe, 1950-2015
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
8
7
6
5
4
3
2
1
0
127947
156418
187330
220631
252587
278220
296091
309546
322695
336920
347735
357844
367346
374617
130727
163036
199824
239841
277484
307546
329004
348602
371836
389004
400407
408773
415468
419026
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
model B
model D
number (left axis)
prevalence of people with DS in the population (per 10,000 inhabitants) (right axis)

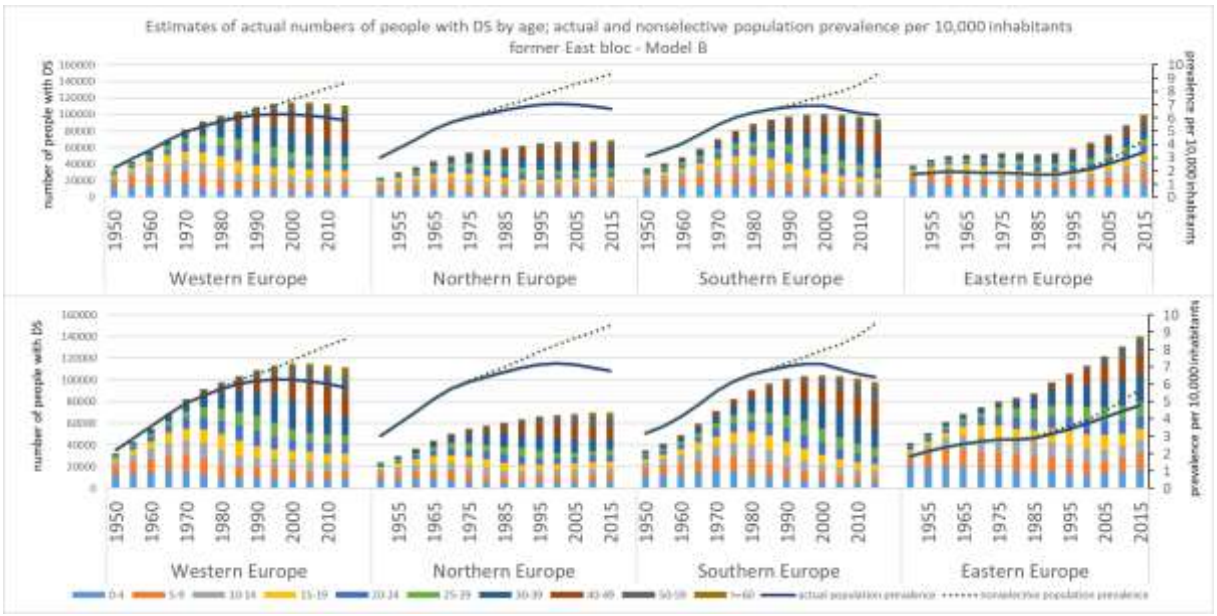

Estimated people with DS in Europe by age group, as of 2015
model B
model D
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
11
10
9
8
7
6
5
4
3
2
1
0
38117
35116
30947
28841
29328
27388
28870
28425
31018
32532
28227
19044
10069
4526
1452
522
195
38118
35218
31299
31769
30014
35014
33951
35176
37849
37649
32250
21984
11593
4938
1483
527
195
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
number (left axis)
population prevalence per 10,000 inhabitants (right axis)

Europe: Some extra graphs

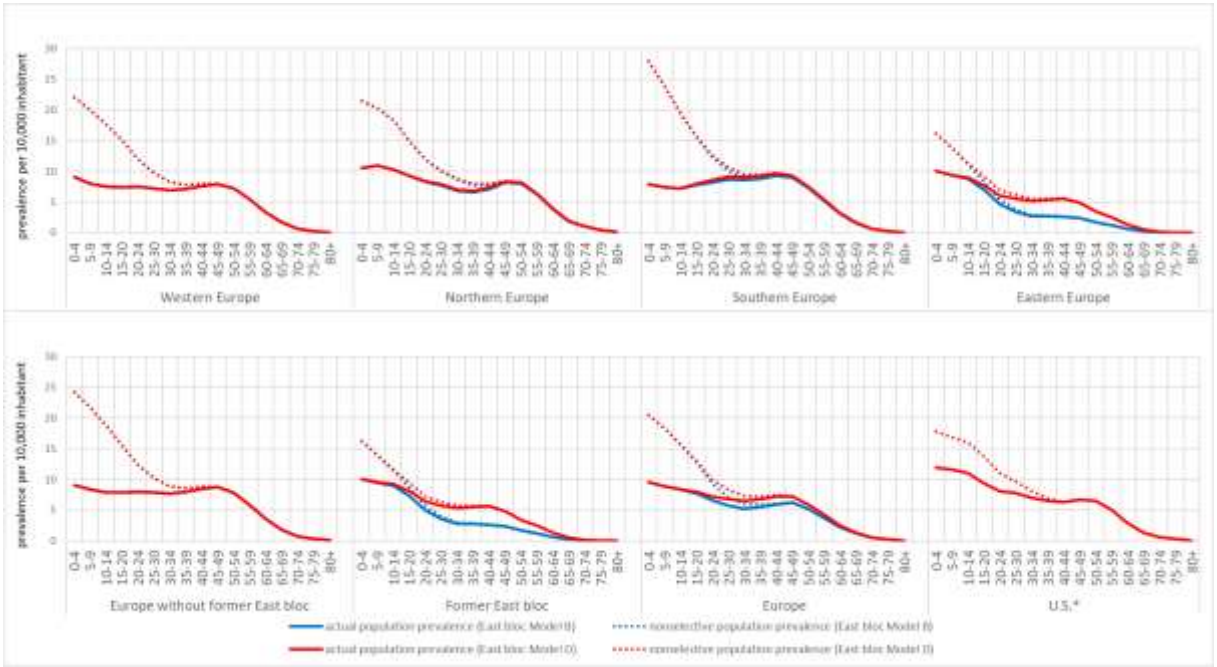
In the main article, the Figure below is presented for Model D. Here are the results for Model B.



9In the main article the Figure below is presented for Model D. Here, we have added Model B for comparison.



Estimates of actual and nonseletive population prevalence per 10,000 inhabitants by age group, Europe and U.S., as of 2015 (former East bloc countries Model D and B for comparison)



S8. Comparison of the model with the GBD approach

In the introduction of the main paper, we mentioned that prior to our study, birth and population numbers of DS for European countries had only been roughly estimated. This referred to the results of the Global Burden of Disease (GBD) Study 2017, which has been previously explained by those authors (Lancet Lond. Engl. 392, 1789–1858 (2018)). Results by country can be found at http://ghdx.healthdata.org/gbd-results-tool. In this section, we compare our approach with GBD.

The estimated total population of people with DS as of 2015 differs between our study and GBD. At the regional level, the total difference is small for former West bloc countries (GBD has an estimation that is 4% less than our model) and very large for former East bloc countries (GBD has a 64% higher estimate than our model). At the country level, for almost all former West bloc countries—with the exception of Luxembourg (+33%), Denmark (+19%), and Portugal (-35%)—the difference between GBD and our model's estimates is less than ±15%. However, for most former East bloc countries, GBD estimates are much higher than our estimates, which probably results from the fact that we have modeled survival for DS before ~2000 in former East bloc countries to be much lower than that of former West bloc countries.

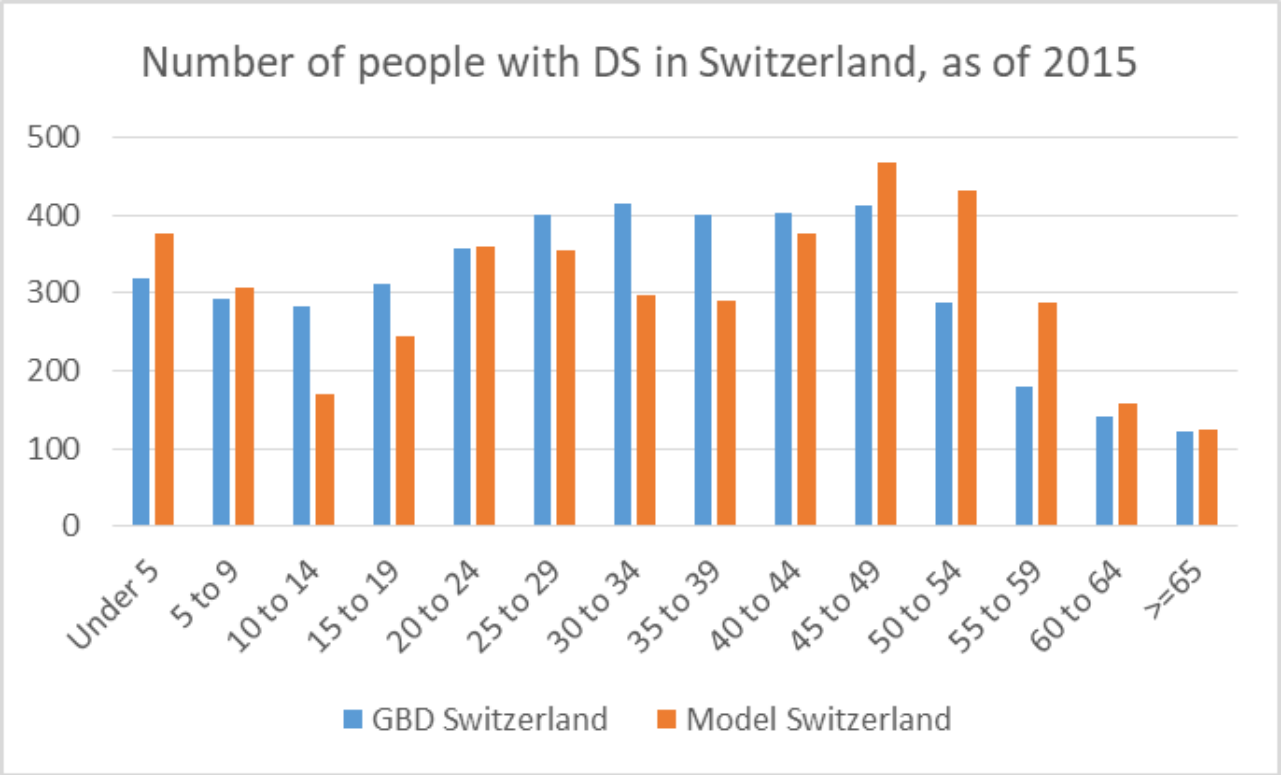
In contrast to our model, the GBD study seems to have assumed a more or less similar historical survival of people with DS in former East bloc versus former West bloc countries. However, as we have seen in Supplementary Materials S5, a model with more or less similar historical survival of people with DS in former East bloc countries as compared to former West bloc countries is highly improbable.

Table S8: Number of people with DS in Europe as of 2015; Model versus GBD estimates

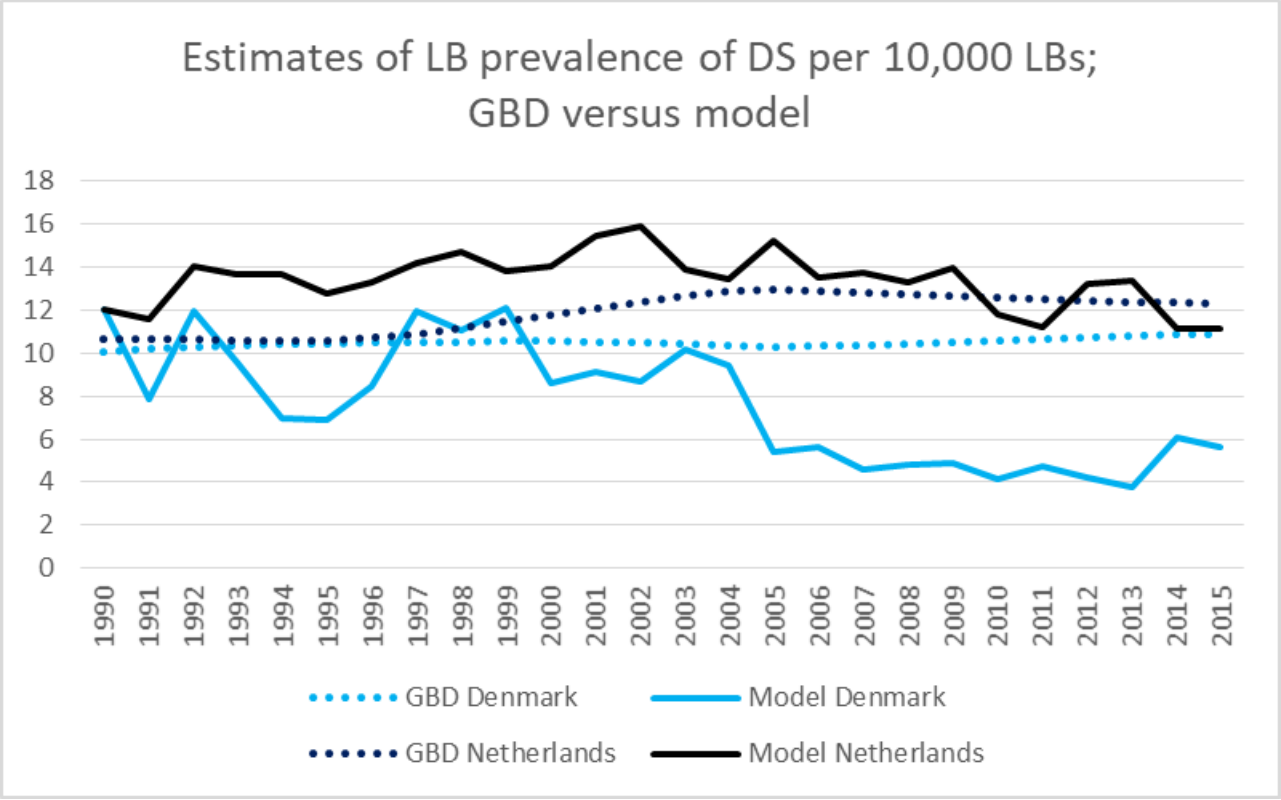
Region/country	Model	GBD	Difference of GBD in relation to our model
Western Europe	**111304**	**109130**	**-2.0%**
Austria	4716	5247	11.3%
Belgium	5646	5102	-9.6%
France	35684	40188	12.6%
Germany	47465	42228	-11.0%
Luxembourg	243	322	32.5%
Netherlands	13309	11725	-11.9%
Switzerland	4241	4318	1.8%
Northern Europe	**69760**	**68659**	**-1.6%**
Denmark	2887	3443	19.3%
Estonia	679	964	42.0%
Finland	4130	4100	-0.7%
Iceland	234	225	-3.8%
Ireland	6557	5675	-13.5%
Latvia	1226	1367	11.5%
Lithuania	2020	1319	-34.7%
Norway	3725	3879	4.1%
Sweden	6792	7191	5.9%
United Kingdom	41511	40496	-2.4%

Southern Europe	**97964**	**88613**	**-9.6%**
Albania	1729	1846	6.8%
Bosnia and Herzegovina	2063	2275	10.3%
Croatia	2232	3154	41.3%
Greece	7035	6017	-14.5%
Italy	38330	35227	-8.1%
Malta	423	407	-3.8%
Montenegro	440	410	-6.8%
North Macedonia	780	1379	76.8%
Portugal	6421	4188	-34.8%
Serbia + Kosovo	5275	4498	-14.7%
Slovenia	913	906	-0.8%
Spain	32323	28306	-12.4%
Eastern Europe	**139997**	**239124**	**70.8%**
Belarus	5161	6767	31.1%
Bulgaria	2879	4308	49.6%
Czech Republic	3299	5771	74.9%
Hungary	3463	6600	90.6%
Poland	21328	33006	54.8%
Republic of Moldova	2041	2829	38.6%
Romania	8736	9085	4.0%
Russian Federation	69220	131383	89.8%
Slovakia	2396	4626	93.1%
Ukraine	21474	34749	61.8%
Former West bloc	**261672**	**248284**	**-5.1%**
Former East bloc	**157354**	**257242**	**63.5%**
Europe	**419026**	**505526**	**20.6%**

Even for countries in which the total DS population estimate is highly similar between the GBD model and ours, the age distribution is not, as illustrated for Switzerland on the next page.

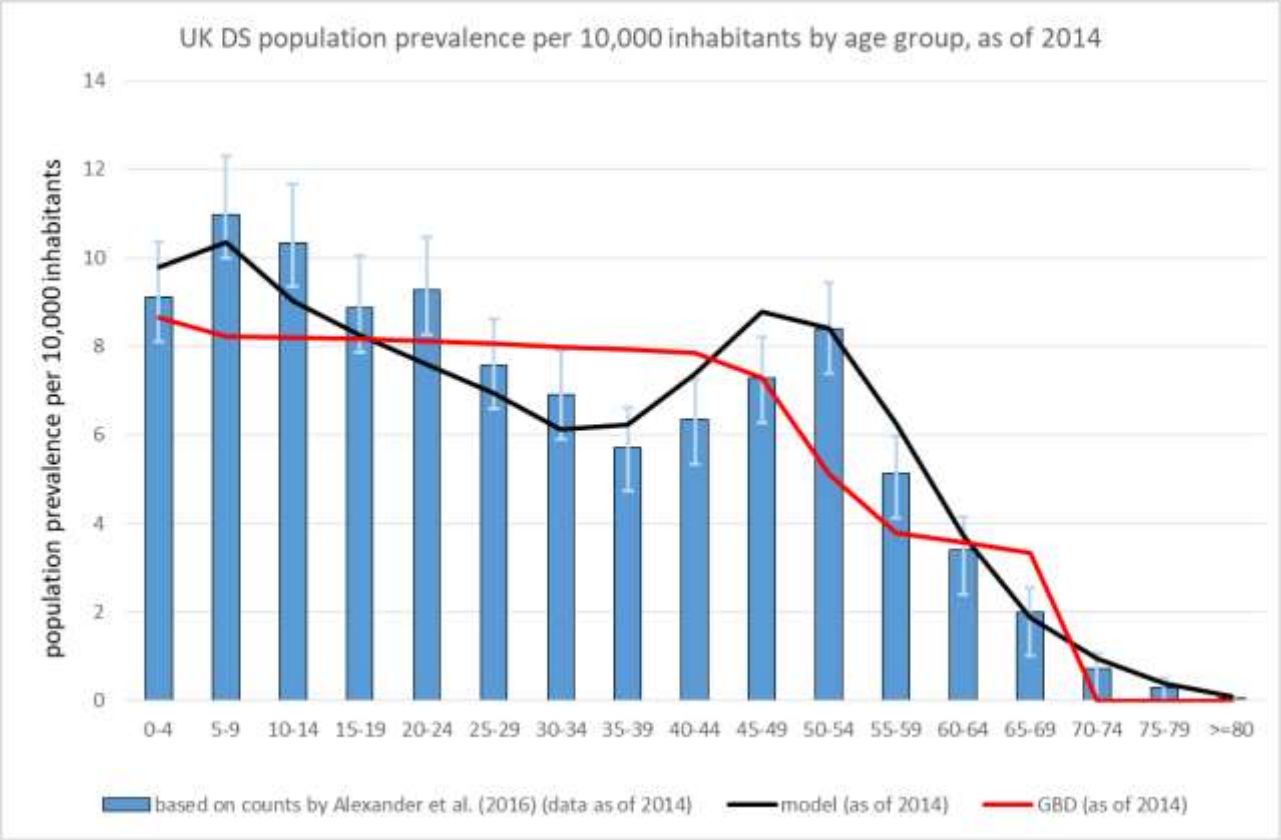


In addition to the differences in modeling survival in former East bloc countries, one of the differences between GBD and our model stems from different input of LBs with DS by year. We consider GBD to be less precise in this respect. For instance, for the Netherlands and Denmark, fairly precise numbers are available (Supplementary Materials S1C and S1D). We have used these precise data; whereas for these and other countries, GBD seems to have used a more rough estimated approach. As can been seen in the Figures below, this leads to differences that can be rather large.



Specific to DS, there also seem to be internal inconsistencies in GBD. For instance, according to GBD, the total population size of people with DS in the Netherlands increased with 1,468 people between 1998–2003. In this period, according to GBD, 1,225 children with DS were born, and 478 people with DS died with DS as primary cause of death. As not all deaths of people with DS will be assigned to DS as primary cause of death, the total number of deaths of people with DS will actually be higher. With 1,225 LBs and at least 478 deaths, the DS population would be expected to have increased with a maximum of 747 persons. However, GBD reports an increase of 1,468, which leaves an extra at least 721 (or 1,468 - 747) unaccounted persons. It is highly unlikely that this difference can be explained by migration of people with DS. Immigration surplus was around 169,000 people total for this period, according to the Dutch Statistical Office (CBS). It is not credible that this accounts for an extra 721 people with DS.

Finally, our model has a better fit with the empirical counts of people with DS who are alive. That is the case for the four former East-bloc countries with data, but for these countries, one could argue that our model has been adapted to fit the data (see Supplementary Materials S5). For the four former West bloc countries with data, we have not adapted to fit the data, as our initial model already had a good fit (Supplementary Materials S5). To illustrate our model's better fit to the data, below, we present the comparison with the 2014-UK study of Alexander et al. (2016) (doi: 10.1111/jir.12277).



S9. Relation between GDP and reduction rates

In the Discussion Section of the main paper, we mentioned that a country's wealth might play a role in the magnitude of reduction rates of DS LBs. In the graph below, we have plotted reduction rates against the average Gross Domestic Product per capita in international dollars at purchasing power parity at current prices for the period 2011-2015, as reported by the International Monetary Fund, World Economic Outlook Database, April 2019 Edition, retrieved on March 2, 2020 at https://www.imf.org/external/pubs/ft/weo/2019/01/weodata/index.aspx.

For all European countries (excluding Ireland and Malta) a logarithmic regression has the best fit. Figure S9A shows that higher GDP correlates with higher reduction rates. However, this effect seems to be limited to countries with a GDP of 35,000 international dollars per capita (current prices, purchasing power parity) or less, where reduction rates range from 8.5% to 83.4%. In countries with higher incomes, reduction rates range from 40.3% to 79.1%. As countries become wealthier, prenatal services and reimbursement of the costs are made more widely available, leading to higher uptake, increased detection, more terminations, and therefore higher reduction rates. In wealthier countries, screening is often universally available and widely accessible. However, there still are differences in reduction rates between wealthier countries, but these appear to be determined primarily by cultural differences rather than economic factors.

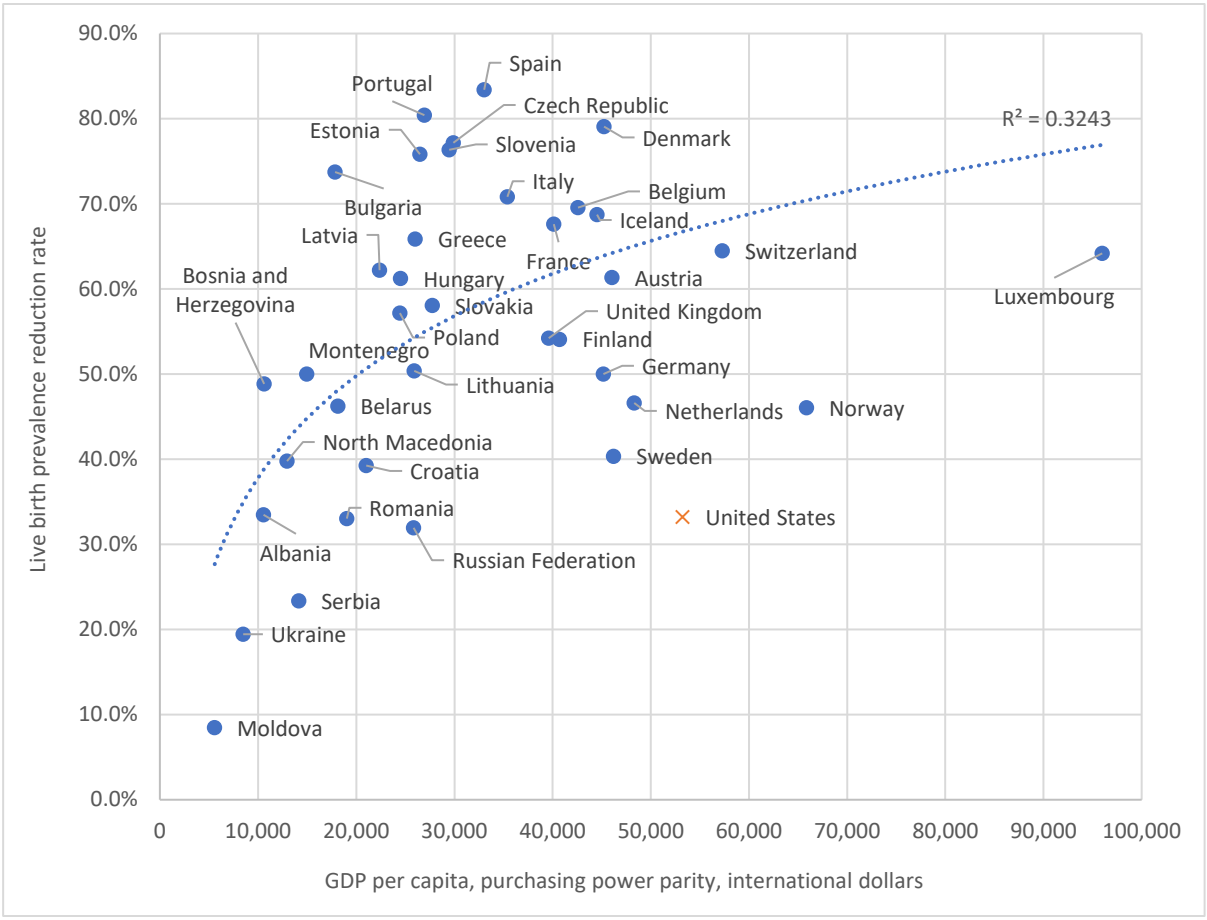


Figure S9A. The relation between GDP and reduction rates in Europe (2011-2015)
Ireland and Malta are excluded from the analysis, as abortions were legally restricted in these countries; U.S. is not in the estimation of the logarithmic regression line, but added for comparative reasons.

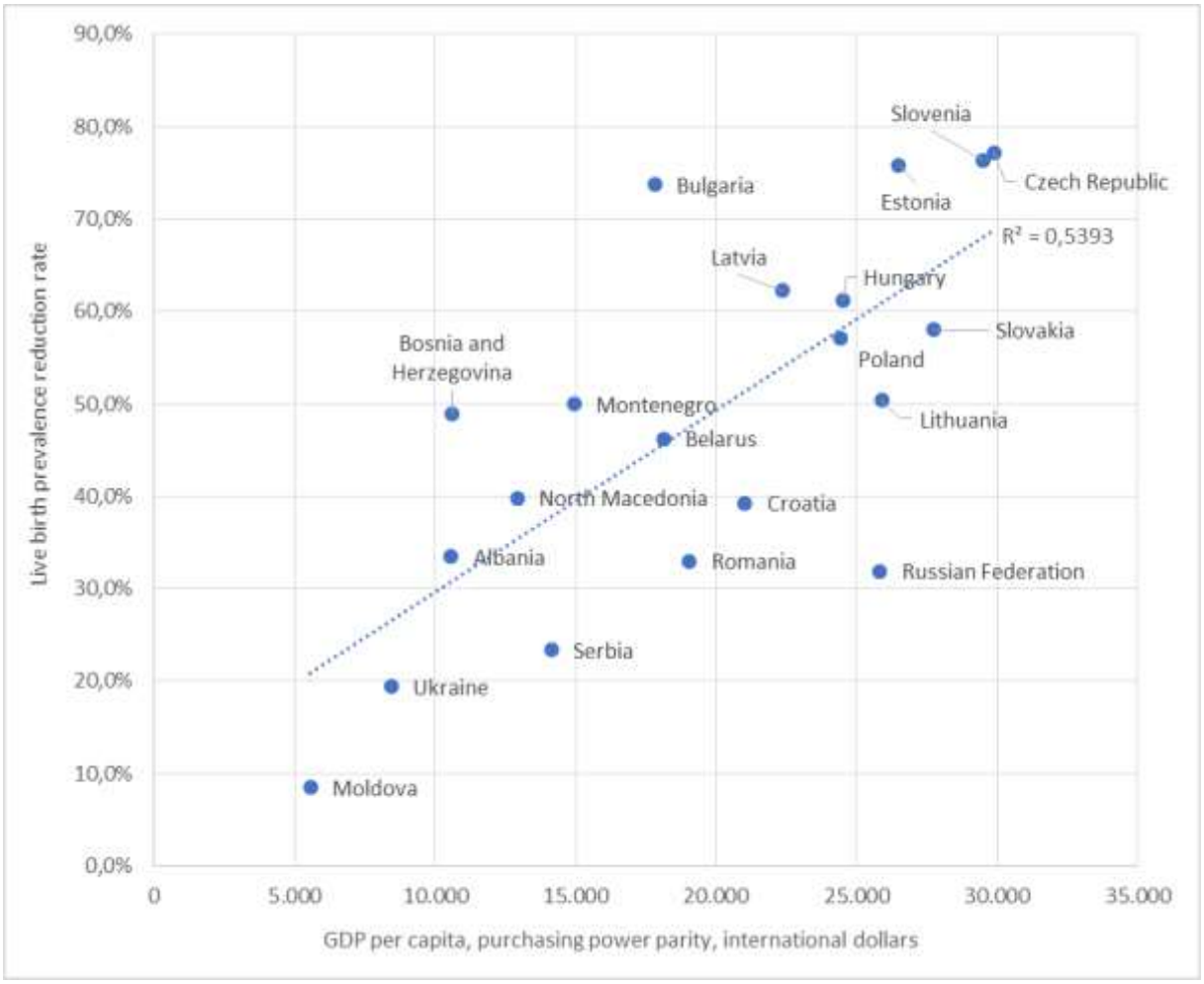


Figure S9B. The relation between GDP and reduction rates in former European East bloc countries (2011-2015)

Between 2011-2015, the overall reduction in former East bloc countries was 38%, compared to 63% for the rest of Europe. Former East bloc countries have lower incomes and, in general, their screening programs have been introduced more recently and are less widely available. We found a strong correlation between Gross Domestic Product per capita (GDP) and reduction rates in these countries ($r = 0.73$; $p < 0.000$), suggesting that prenatal screening availability and uptake increases as countries and citizens become wealthier. In Figure S9B, this strong relation ($R^2 = 0.54$) is shown.

For former West bloc countries, there is no significant relation between GDP and reduction rates. In wealthier countries, differences between reduction rates are not economically determined.

It should be noted that while, in general, reduction rates rise with growing national income up to a certain level, this does not imply that LB prevalence of DS declines at the same rate. Average maternal age is also positively correlated with GDP per capita, and therefore the expected/nonselective live birth prevalence of Down syndrome rises as countries become wealthier (correlation between nonselective LB prevalence and GDP per capita, as of 2011-2015: $r = 0.70$; $p < 0.000$). As a result of both reduction rates and nonselective LB prevalence increasing with GDP per capita, as of 2011-2015, there is no significant correlation between GDP per capita and actual LB prevalence.